

The Implications of Recent Data Sets for the Management of Hepatocellular Carcinoma

*A Live Post-ESMO GI and Post-ASCO CME/MOC-Accredited Webcast
and Multifaceted Enduring Resource*

Thursday, July 27, 2023

5:00 PM – 6:00 PM ET

Faculty

Ghassan Abou-Alfa, MD, MBA

Daneng Li, MD

Moderator

Neil Love, MD

Faculty



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Memorial Sloan Kettering Cancer Center
Professor
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Moderator
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Research To Practice



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Duarte, California

Commercial Support

This activity is supported by an educational grant from AstraZeneca Pharmaceuticals LP.

Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BeyondSpring Pharmaceuticals Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI BioPharma Corp, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Corporation, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab US Inc, Gilead Sciences Inc, Grail Inc, GSK, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Kronos Bio Inc, Legend Biotech, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, MEI Pharma Inc, Merck, Mersana Therapeutics Inc, Mirati Therapeutics Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC, SpringWorks Therapeutics Inc, Stemline Therapeutics Inc, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, TerSera Therapeutics LLC, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc, and Zymeworks Inc.

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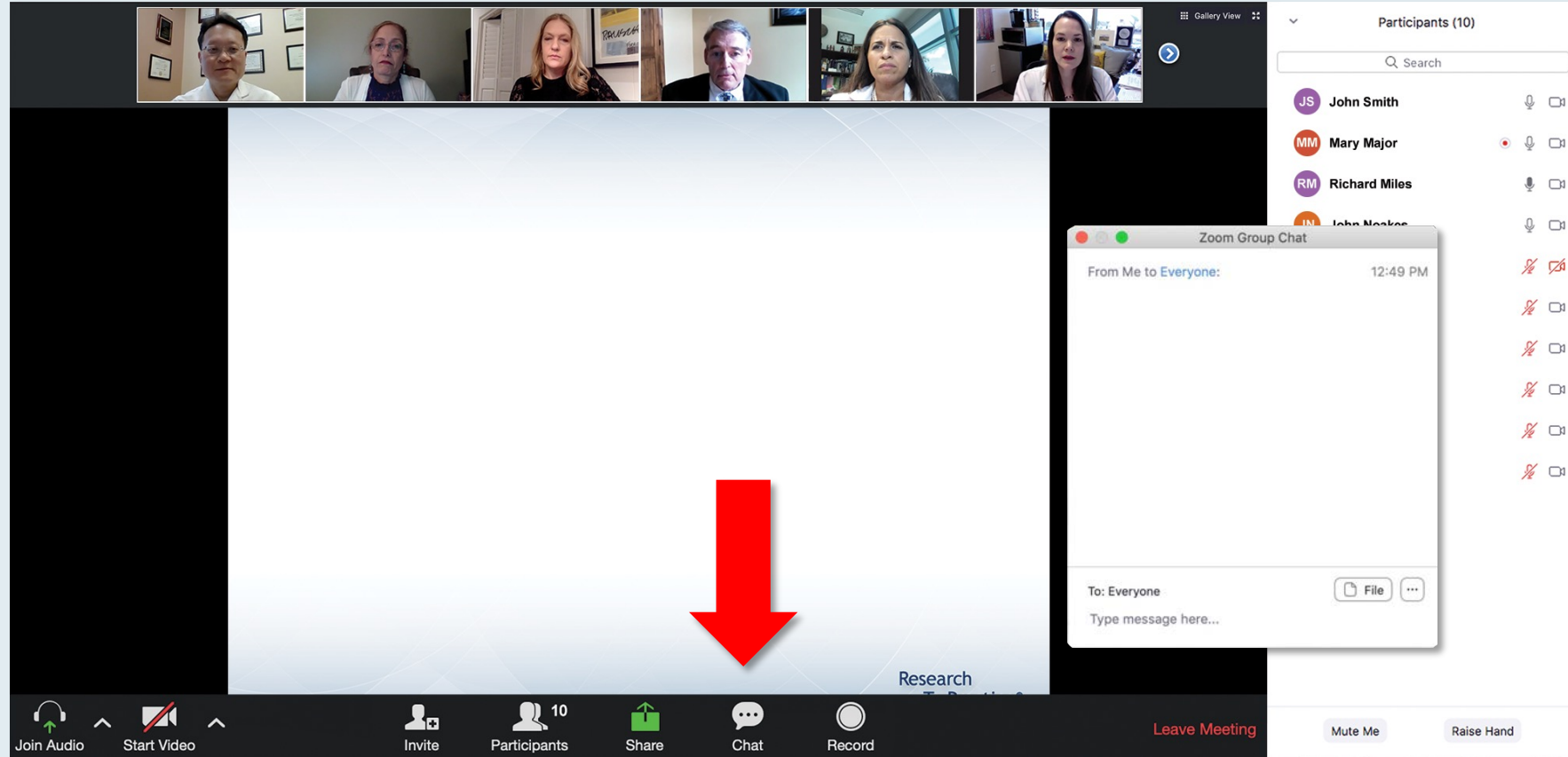
Dr Abou-Alfa — Disclosures

Consulting Agreements	Astellas, AstraZeneca Pharmaceuticals LP, Autem Medical, Berry Genomics, BioNTech SE, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Eisai Inc, Exelixis Inc, FibroGen Inc, Genentech, a member of the Roche Group, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Merck, Merus BV, Neogene Therapeutics, Novartis, Servier Pharmaceuticals LLC, Tempus, Thetis Pharmaceuticals, Vector Pharma, Yiviva
Contracted Research	Agenus Inc, Arcus Biosciences, AstraZeneca Pharmaceuticals LP, BioNTech SE, Bristol Myers Squibb, Digestive Care Inc, Elicio Therapeutics, Genentech, a member of the Roche Group, Helsinn Healthcare SA, Puma Biotechnology Inc, QED Therapeutics, Yiviva
Nonrelevant Financial Relationship	Parker Institute for Cancer Immunotherapy

Dr Li — Disclosures

Consulting Agreements	Coherus BioSciences, Delcath Systems Inc, Eisai Inc, Exelixis Inc, Genentech, a member of the Roche Group, Ipsen Biopharmaceuticals Inc, Merck, Servier Pharmaceuticals LLC, TerSera Therapeutics LLC
Contracted Research	AstraZeneca Pharmaceuticals LP, Brooklyn ImmunoTherapeutics

We Encourage Clinicians in Practice to Submit Questions



Feel free to submit questions now before the program begins and throughout the program.

Familiarizing Yourself with the Zoom Interface

Expand chat submission box

The screenshot shows a Zoom meeting interface. At the top, there are video thumbnails for participants: RTP Coordinat..., Kirsten Miller, RTP Mike Rivera, and Lisa Suarez. Below the thumbnails is a slide titled "Meet The Professor Program Participating Faculty" featuring six faculty members with their photos and titles:

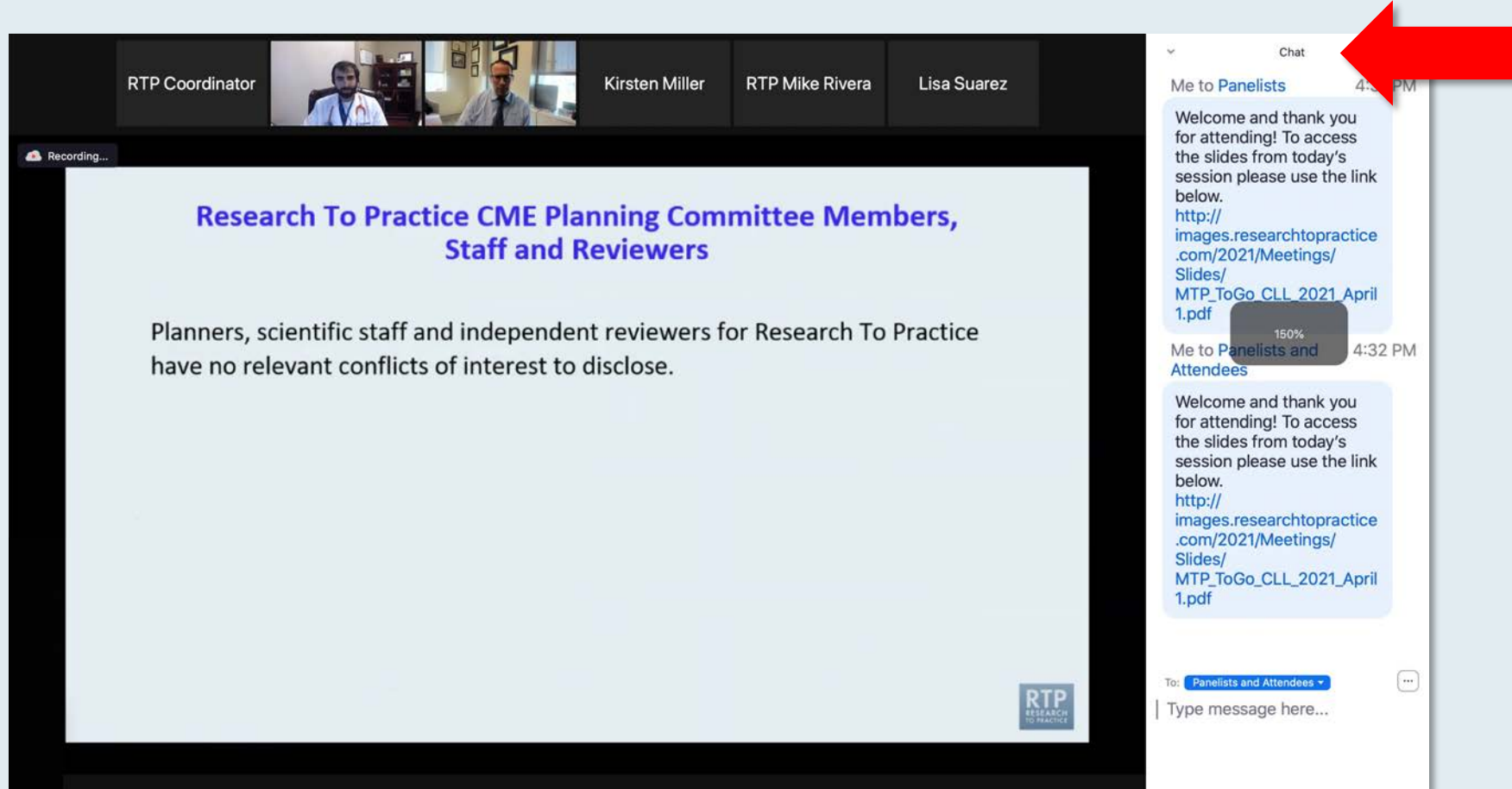
- Nancy L Bartlett, MD**
Professor of Medicine
Koman Chair in Medical Oncology
Washington University School of Medicine
St Louis, Missouri
- Jonathan W Friedberg, MD, MMSc**
Samuel E Durand Professor of Medicine
Director, James P Wilmot Cancer Institute
University of Rochester
Rochester, New York
- Carla Casulo, MD**
Associate Professor of Medicine
Division of Hematology/Oncology
Director, Hematology/Oncology Fellowship Program
University of Rochester
Wilmot Cancer Institute
Rochester, New York
- Brian T Hill, MD, PhD**
Director, Lymphoid Malignancy Program
Cleveland Clinic Taussig Cancer Institute
Cleveland, Ohio
- Christopher R Flowers, MD, MS**
Chair, Professor
Department of Lymphoma/Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas
- Brad S Kahl, MD**
Professor of Medicine
Washington University School of Medicine
Director, Lymphoma Program
Siteman Cancer Center
St Louis, Missouri

On the right side of the interface is a chat window. It shows two messages from "Me to Panelists" and "Me to Panelists and Attendees" at 4:31 PM and 4:32 PM respectively. The messages contain a welcome message and a link to a PDF file. At the bottom of the chat window, there is a "To:" dropdown menu set to "Panelists and Attendees" and a text input field labeled "Type message here...". A red arrow points to the white line above the text input field, indicating where to drag to expand the submission box.

Drag the white line above the submission box up to create more space for your message.

Familiarizing Yourself with the Zoom Interface

Increase chat font size



The screenshot displays a Zoom meeting interface. At the top, a gallery view shows participants: RTP Coordinator, Kirsten Miller, RTP Mike Rivera, and Lisa Suarez. The main area shows a presentation slide titled "Research To Practice CME Planning Committee Members, Staff and Reviewers" with the text: "Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose." A "Recording..." indicator is visible in the top left of the slide area. On the right, the chat window is open, showing a message from "Me to Panelists" with a link to a PDF. A red arrow points to the font size control (a small square with "150%") in the chat window's header. The chat input field at the bottom says "Type message here..." and the "To:" dropdown is set to "Panelists and Attendees".

**Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.**

Clinicians in the Audience, Please Complete the Pre- and Postmeeting Surveys

The screenshot shows a Zoom meeting window. At the top, a row of seven participant video thumbnails is visible. The main content area on the left displays a presentation slide with the following text:
Meet The Professionals
Optimizing the Selection and Sequencing of Therapy for Patients with Metastatic Gastrointestinal Cancer
Wednesday, August 25, 2022
5:00 PM – 6:00 PM EST
Faculty
Wells A Messersmith, MD
Moderator
Neil Love, MD
The RTP Research to Practice logo is in the bottom right corner of the slide. A 'Quick Survey' pop-up window is centered over the slide, listing several treatment combinations with radio button options. To the right of the main content area is a 'Participants (10)' sidebar showing a list of names with their respective status icons (mute, video on/off). At the bottom of the window is a Zoom toolbar with icons for Join Audio, Start Video, Invite, Participants, Share, Chat, Record, and a red 'Leave Meeting' button.

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RTP
RESEARCH TO PRACTICE

Quick Survey

- ☐ Certizomib +/- dexamethasone
- ☐ Pomalidomide +/- dexamethasone
- ☐ Certizomib + pomalidomide +/- dexamethasone
- ☐ Elotuzumab + lenalidomide +/- dexamethasone
- ☐ Elotuzumab + pomalidomide +/- dexamethasone
- ☐ Daratumumab + lenalidomide +/- dexamethasone
- ☐ Daratumumab + pomalidomide +/- dexamethasone
- ☐ Daratumumab + bortezomib +/- dexamethasone
- ☐ Isaxomib + Rd
- ☐ Other

Submit

Participants (10)

- JS John Smith
- MM Mary Major
- RM Richard Miles
- JN John Noakes
- AS Alice Suarez
- JP Jane Perez
- RS Robert Stiles
- JF Juan Fernandez
- AK Ashok Kumar
- JS Jeremy Smith

Join Audio Start Video Invite Participants Share Chat Record Leave Meeting

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Regulatory and reimbursement issues aside, which treatment would you recommend for a 65-year-old patient with clear cell renal cell carcinoma (ccRCC) who has been on a TKI for 3 years and follow-up 3 years later is found to have asymptomatic (PS 0)?
The slide lists eight options:
1. Nivolumab/ipilimumab
2. Avelumab/axitinib
3. Pembrolizumab/axitinib
4. Pembrolizumab/lenvatinib
5. Nivolumab/cabozantinib
6. Tyrosine kinase inhibitor (TKI) monotherapy
7. Anti-PD-1/PD-L1 monotherapy
8. Other
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ONCOLOGY TODAY

WITH DR NEIL LOVE

Management of Hepatocellular Carcinoma



PROFESSOR ARNDT VOGEL
HANNOVER MEDICAL SCHOOL



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Inside the Issue: Exploring the Current and Future Management of High-Risk, Hormone-Sensitive Nonmetastatic Prostate Cancer

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Monday, July 31, 2023

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Inside the Issue: The Current and Future Role of CD20 x CD3 Bispecific Antibodies in the Management of Non-Hodgkin Lymphoma

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Optimizing the Management of Melanoma

**Thursday, August 10, 2023
5:00 PM – 6:00 PM ET**

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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Memorial Sloan Kettering Cancer Center
Professor
Weill Cornell Medical College at Cornell University
Adjunct Professor
Trinity College Dublin (Ireland)
New York, New York

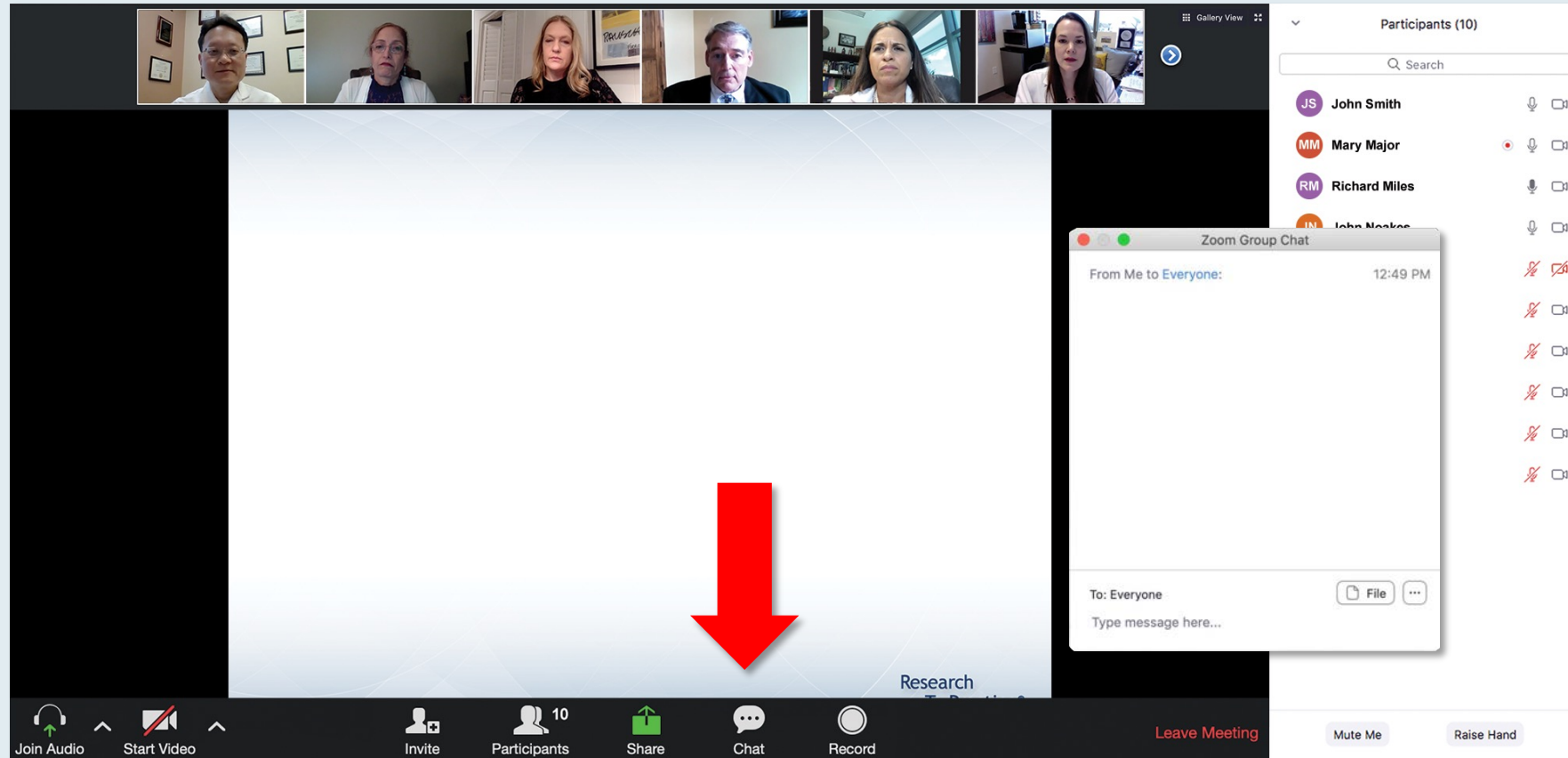


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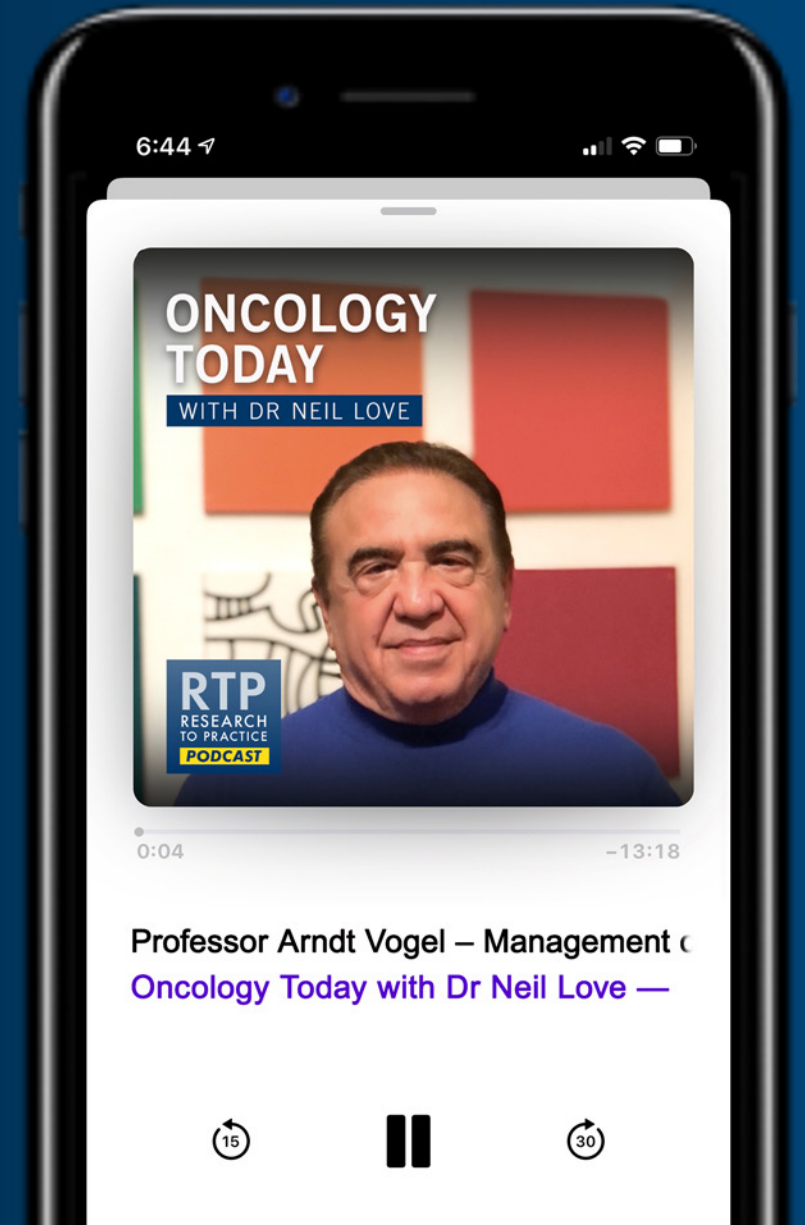
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First-Line Therapy for Advanced Hepatocellular Carcinoma (HCC)

Ghassan Abou-Alfa
Memorial Sloan Kettering Cancer Center

Post Conference 2023 HCC live webinar
July 27, 2023

Second and Later-Line Therapy for Advanced HCC

Daneng Li, M.D.
Associate Professor
Department of Medical Oncology and Therapeutics Research
City of Hope Comprehensive Cancer Center

Agenda

INTRODUCTION: Etiology of Hepatocellular Carcinoma (HCC) and IO Response

MODULE 1: First-Line Therapy for Advanced HCC – Dr Abou-Alfa

MODULE 2: Second- and Later-Line Therapy for Advanced HCC; Emerging Considerations for Patients with Resectable HCC – Dr Li

Agenda

INTRODUCTION: Etiology of Hepatocellular Carcinoma (HCC) and IO Response

MODULE 1: First-Line Therapy for Advanced HCC – Dr Abou-Alfa

MODULE 2: Second- and Later-Line Therapy for Advanced HCC; Emerging Considerations for Patients with Resectable HCC – Dr Li

FDA-Approved Systemic Therapy for Advanced HCC

2007

2008

2009

2010

2011

2012

2013

2014

2015

2016

2017

2018

2019

2020

2021

2022

Sorafenib

First Line

Lenvatinib

Atezolizumab + bevacizumab

Durvalumab/Tremelimumab^^

Second Line and Beyond

Regorafenib

Nivolumab*#

Pembrolizumab*

Cabozantinib

Ramucirumab

Nivolumab + ipilimumab*

*Accelerated FDA approval

*#Accelerated approval withdrawn

^^ Regular FDA approval

Agenda

INTRODUCTION: Etiology of Hepatocellular Carcinoma (HCC) and IO Response

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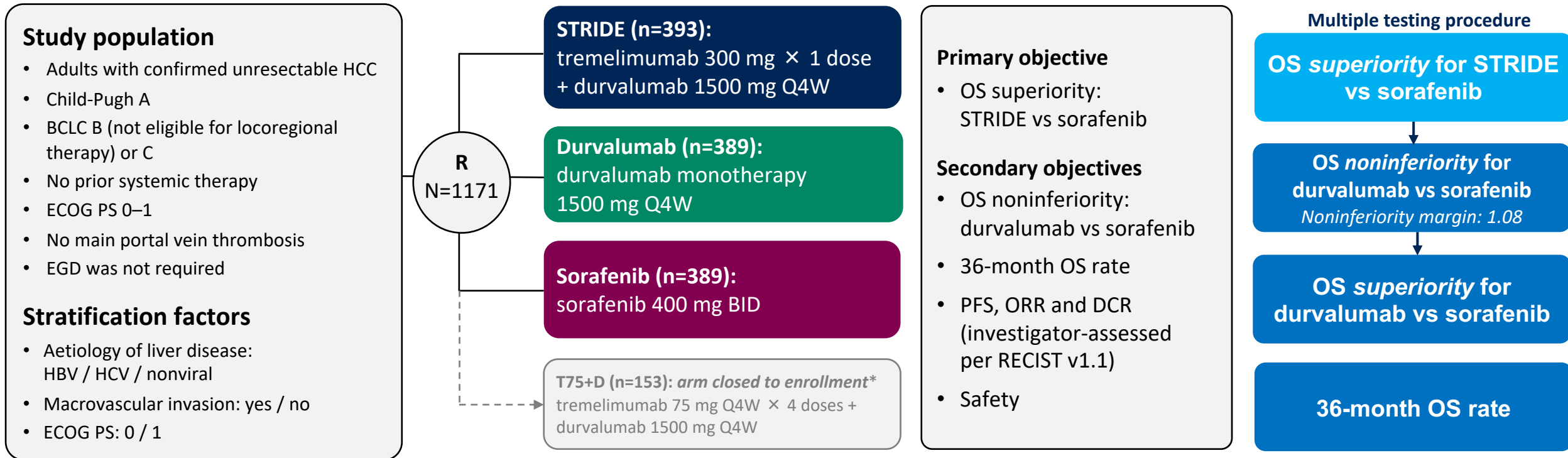
First-Line Therapy for Advanced Hepatocellular Carcinoma (HCC)

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Memorial Sloan Kettering Cancer Center

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HIMALAYA Study Design

HIMALAYA is an open-label, multicenter, global, Phase 3 trial¹

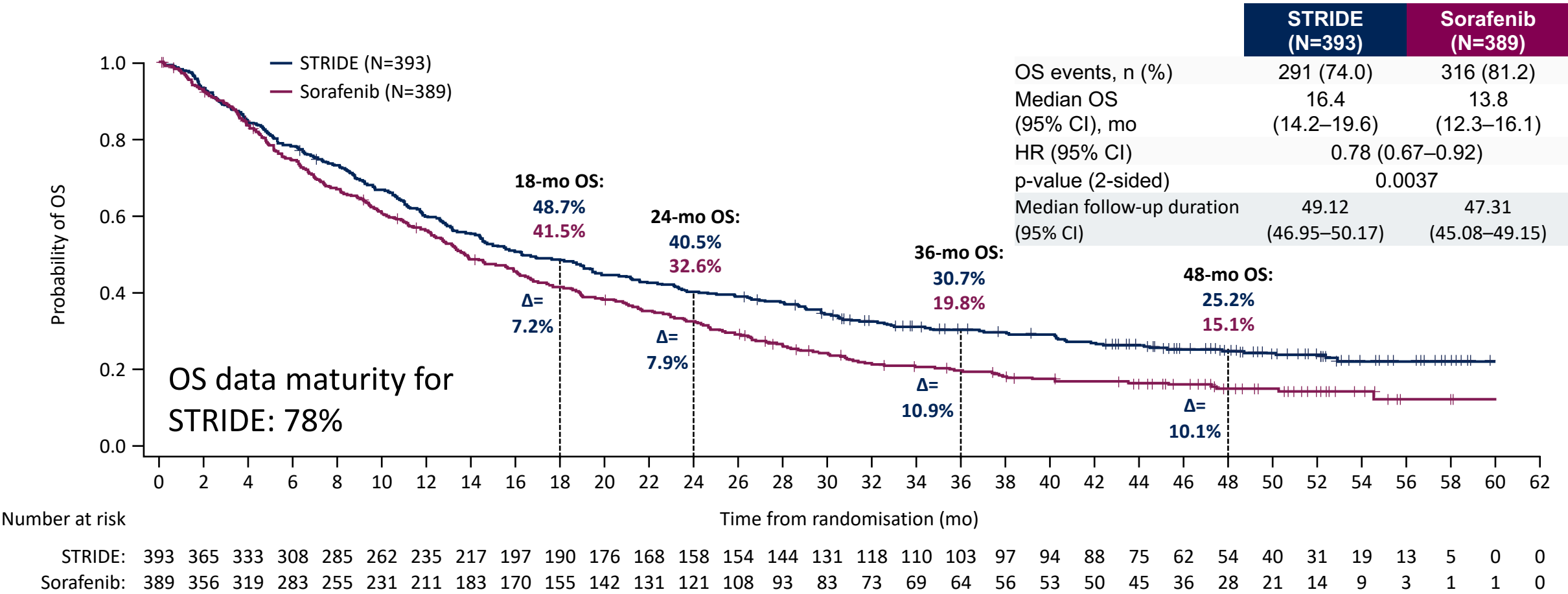


BCLC, Barcelona Clinic Liver Cancer; BID, twice a day; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; EGD, esophagogastroduodenoscopy; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q4W, every 4 weeks; R, randomised; RECIST, Response Evaluation Criteria in Solid Tumours; T75+D, tremelimumab 75 mg Q4W × 4 doses + durvalumab 1500 mg Q4W. *The T75+D arm was closed to enrollment following a preplanned analysis of a Phase 2 study. Participants randomized to this arm (n=153) could continue treatment following arm closure. Results from this arm are not reported in this presentation.

1. Abou-Alfa GK, et al. NEJM Evid 2022;1:EVIDo2100070.

HIMALAYA: Four-year updated OS for STRIDE versus sorafenib

STRIDE demonstrated an unprecedented one in four survival rate at 4 years



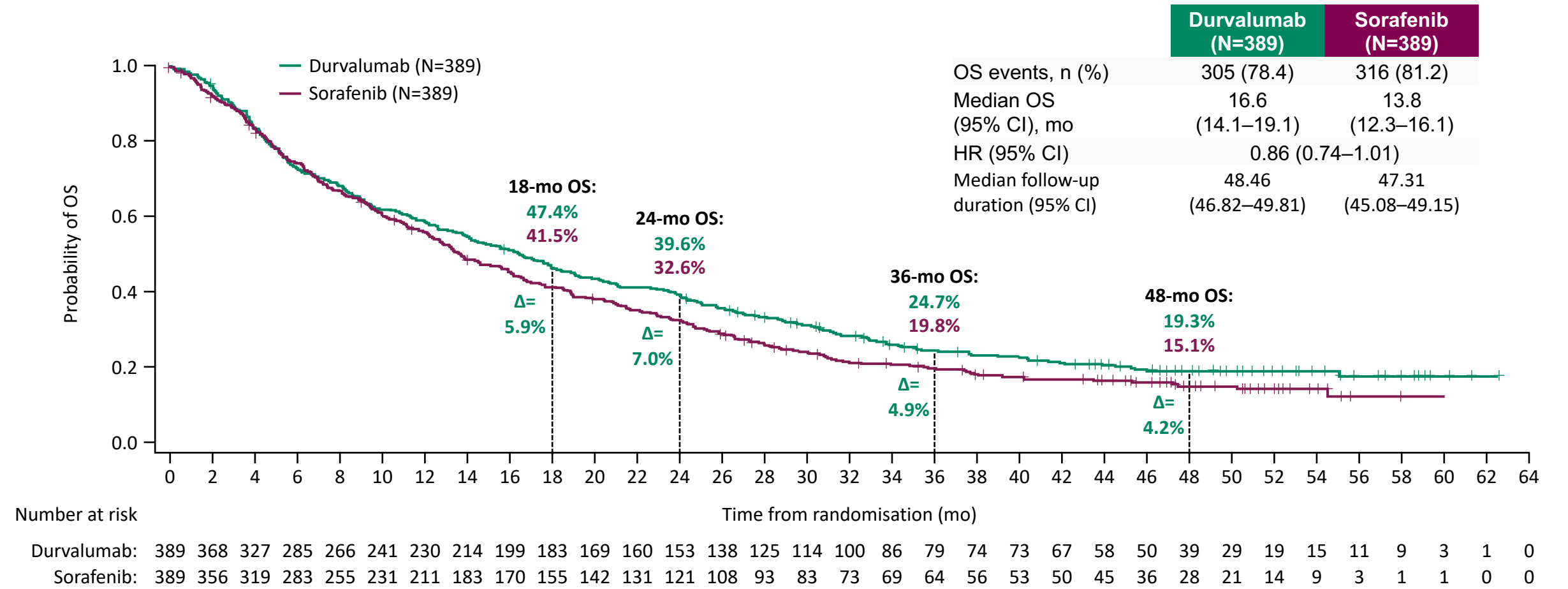
	STRIDE (N=393)	Sorafenib (N=389)
OS events, n (%)	291 (74.0)	316 (81.2)
Median OS	16.4	13.8
(95% CI), mo	(14.2–19.6)	(12.3–16.1)
HR (95% CI)	0.78 (0.67–0.92)	
p-value (2-sided)	0.0037	
Median follow-up duration	49.12	47.31
(95% CI)	(46.95–50.17)	(45.08–49.15)

OS HRs and 95% CIs were calculated using a Cox proportional hazards model adjusting for treatment, aetiology, ECOG performance status, and macrovascular invasion. The 36-mo OS rate had a nominal 2-sided p-value of 0.0006. Updated analysis data cut-off: 23 January 2023.

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; mo, month; OS, overall survival.

HIMALAYA: Four-year updated OS for durvalumab versus sorafenib

With further follow-up, durvalumab maintained noninferiority to sorafenib, consistent with the primary analysis¹



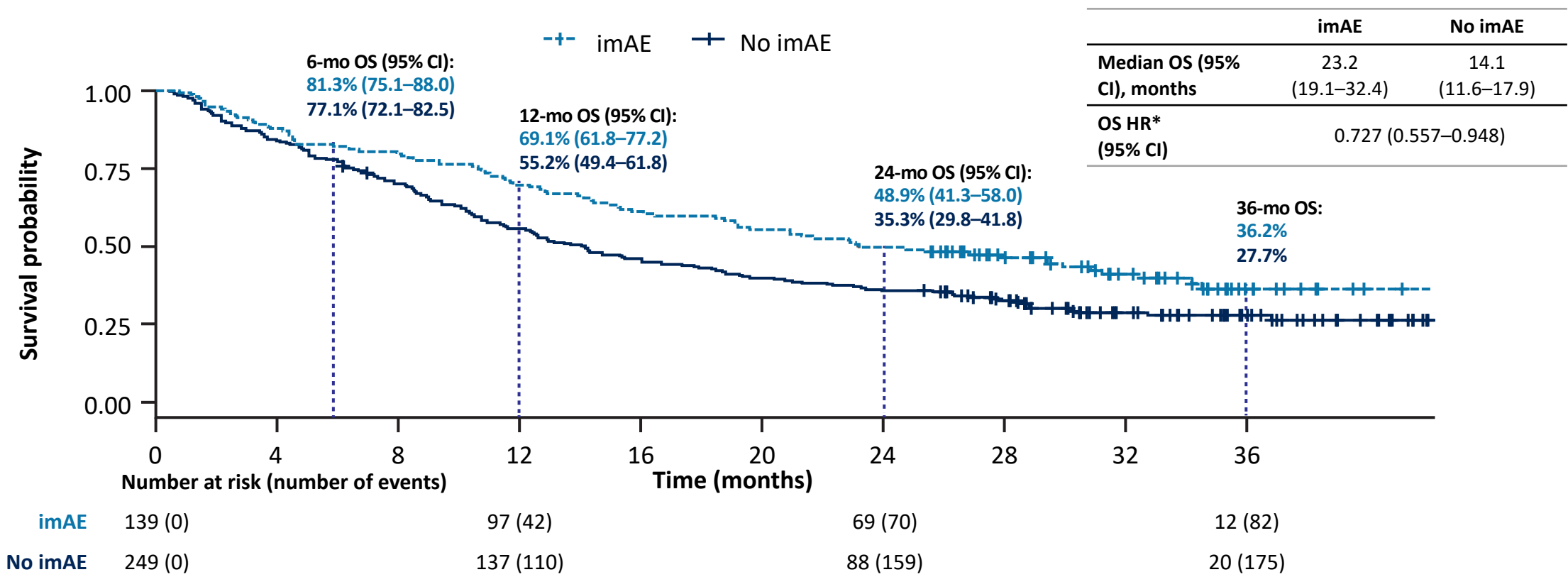
OS HRs and 95% CIs were calculated using a Cox proportional hazards model adjusting for treatment, aetiology, ECOG performance status, and macrovascular invasion. Noninferiority margin = 1.08. Updated analysis data cut-off: 23 January 2023.

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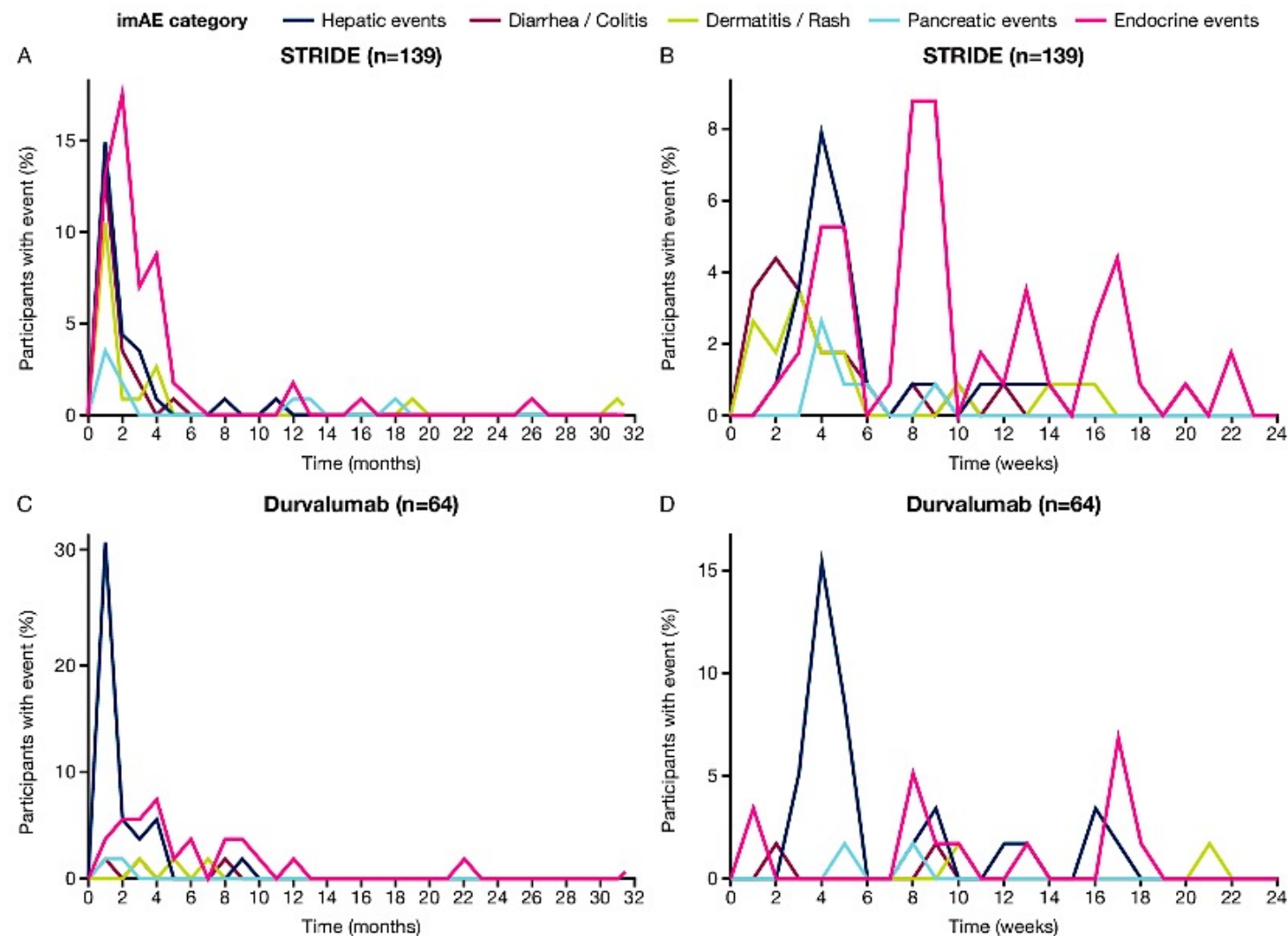
HIMALAYA: OS by imAE Occurrence for STRIDE

An improvement in OS was observed in participants who had an imAE versus those who did not



CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; imAE, immune-mediated adverse event; OS, overall survival. *OS HRs and 95% CIs were calculated using Cox modeling, with imAEs as a time-varying covariate and stratified by etiology, ECOG (0/1), and macro-vascular invasion (yes/no) for participants with versus without imAEs of any grade.

HIMALAYA: imAE Temporal Patterns



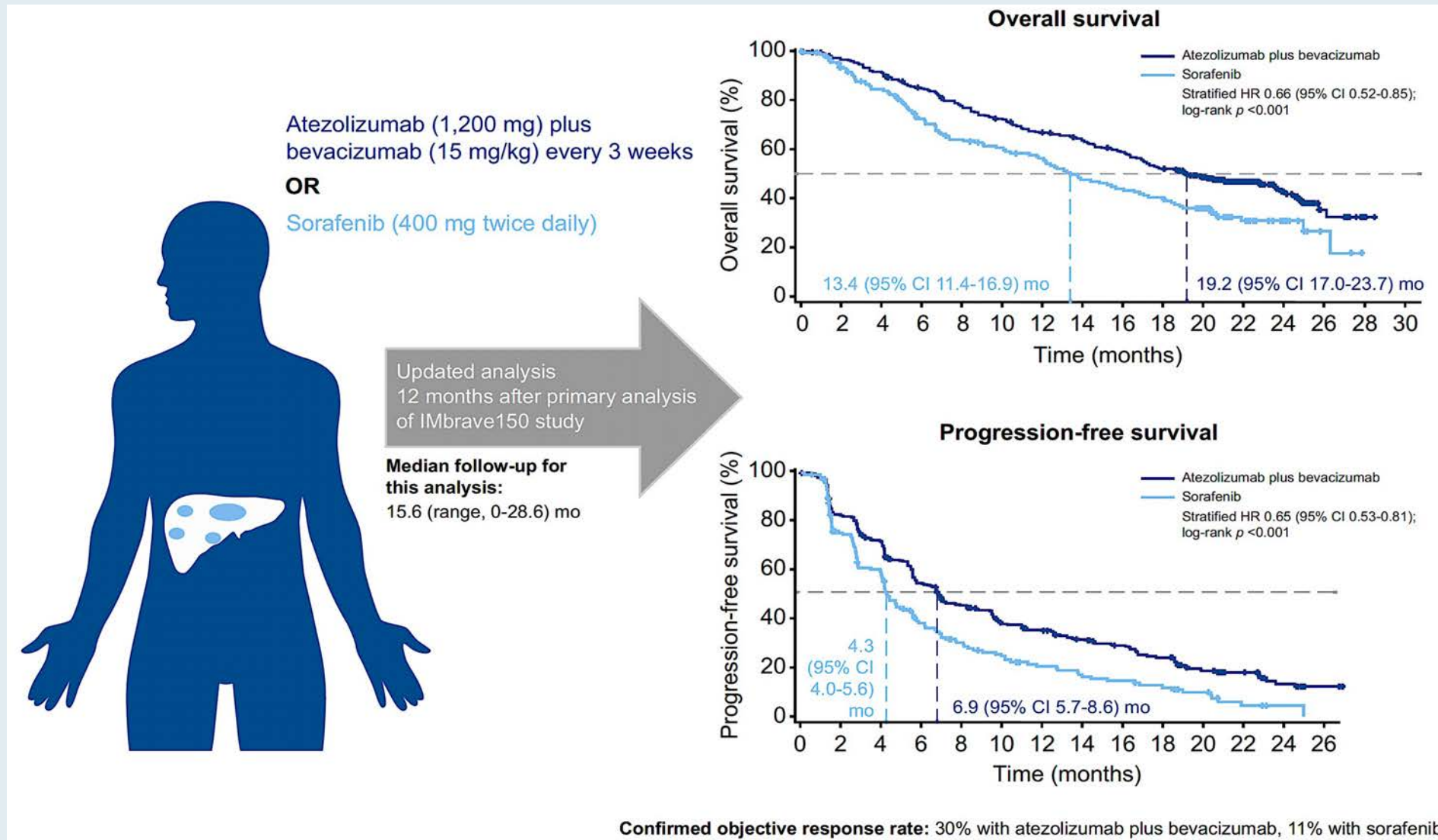
The percentage of participants with an event is the number of participants who experienced at least 1 imAE at each time interval divided by the number of participants who experienced at least 1 imAE at any time. The figure includes the first imAEs only, regardless of grade. Panels A and C plot the total frequency of imAEs each month and panels B and D plot the total frequency of imAEs each week of the month for the first 6 months. imAE, immune-mediated adverse event.

Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma







Ann-Lii Cheng^{1,*}, Shukui Qin², Masafumi Ikeda³, Peter R. Galle⁴, Michel Ducreux⁵,
Tae-You Kim⁶, Ho Yeong Lim⁷, Masatoshi Kudo⁸, Valeriy Breder⁹, Philippe Merle¹⁰,
Ahmed O. Kaseb¹¹, Daneng Li¹², Wendy Verret¹³, Ning Ma¹⁴, Alan Nicholas¹⁵, Yifan Wang¹⁶,
Lindong Li¹⁷, Andrew X. Zhu^{18,19}, Richard S. Finn^{20,*}

2022;76(4):862-73.

IMbrave150 Trial: Updated OS and PFS with Atezolizumab and Bevacizumab (Median Follow-Up 15.6 Months)



IMbrave150 Update: Subgroup Analysis of OS with Atezolizumab and Bevacizumab (Median Follow-Up 15.6 Months)

Subgroup	Atezolizumab plus bevacizumab		Sorafenib		Hazard ratio for death (95% CI)	
	Events/ patients	Median OS, months (95% CI)	Events/ patients	Median OS, months (95% CI)		
Etiology						
Hepatitis B	86/164	19.0 (16.1-NE)	46/76	12.4 (6.7-16.9)		0.58 (0.40-0.83)
Hepatitis C	31/72	24.6 (19.8-NE)	24/36	12.6 (7.4-18.4)		0.43 (0.25-0.73)
Non-viral	63/100	17.0 (11.7-22.8)	30/53	18.1 (11.7-26.3)		1.05 (0.68-1.63)
PD-L1 status						
TC or IC ≥1%	44/86	22.8 (17.0-NE)	24/36	12.6 (7.4-17.1)		0.52 (0.32-0.87)
TC and IC <1%	27/49	19.9 (13.9-NE)	17/28	15.4 (11.4-26.3)		0.81 (0.44-1.49)
Unknown	109/201	18.0 (16.1-24.0)	59/101	13.4 (9.7-18.6)		0.69 (0.50-0.94)

FDA-Approved Anti-VEGF-Directed Monotherapy for HCC

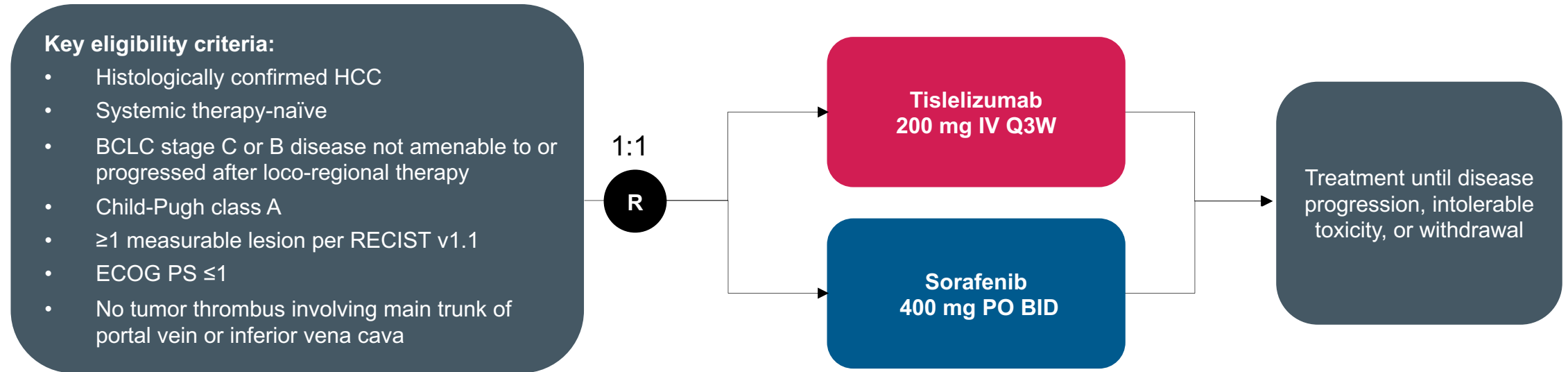
Approved line of therapy	Agent	Study	Primary outcomes
First line	Sorafenib¹	Sorafenib vs placebo (N = 602) Phase III SHARP trial	TTP 4.1 mo vs 4.9 mo mOS 10.7 mo vs 7.9 mo
	Lenvatinib²	Lenvatinib vs sorafenib (N = 954) Phase III REFLECT trial	mPFS 7.4 mo vs 3.7 mo mOS 13.6 mo vs 12.3 mo
Second line	Regorafenib³	Regorafenib vs placebo (N = 573) Phase III RESORCE trial	mPFS 3.1 mo vs 1.5 mo mOS 10.7 mo vs 7.9 mo
	Cabozantinib⁴	Cabozantinib vs placebo (N = 707) Phase III CELESTIAL trial	mPFS 5.2 mo vs 1.9 mo mOS 10.2 mo vs 8.0 mo
	Ramucirumab⁵	Ramucirumab vs placebo (N = 565) Phase III REACH-2 trial	mPFS 2.8 mo vs 1.6 mo mOS 8.5 mo vs 7.3 mo

TTP = time to progression; mOS = median overall survival; mPFS = median progression-free survival

¹ Llovet JM et al. *N Engl J Med* 2008;359(4):378-90; ² Kudo M et al. *Lancet* 2018;391(10126):1163-73; ³ Bruix J et al. *Lancet* 2017;389(10064):56-66; ⁴ Abou-Alfa GK et al. *N Engl J Med* 2018;379(1):54-63; ⁵ Zhu AX et al. *Lancet Oncol* 2019;20(2):282-96.

RATIONALE-301: Phase III Study Design

- Randomized, open-label, multicenter, multiregional phase 3 study

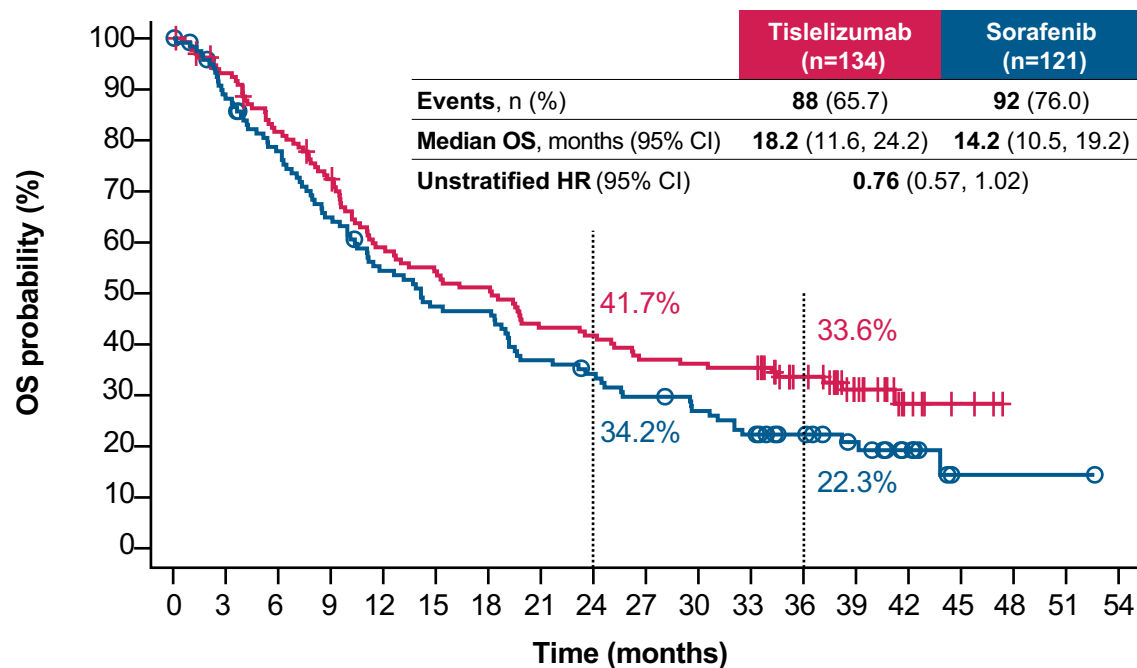


- **Primary endpoint:** OS in the ITT population
- **Key secondary endpoints:** ORR, PFS, and DoR by BIRC per RECIST v1.1, and safety
- **Stratification factors:** Macrovascular invasion (present vs absent), extrahepatic spread (present vs absent), ECOG PS (0 vs 1), etiology (HCV vs other^a), geography (Asia [excluding Japan] vs Japan vs rest of world [EU/US])

^aIncludes HBV. Abbreviations: BCLC, Barcelona Clinic Liver Cancer; BID, twice daily; BIRC, blinded independent review committee; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EU, Europe; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ITT, intent-to-treat; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; Q3W, once every 3 weeks; R, randomized; RECIST, Response Evaluation Criteria In Solid Tumors; US, United States, v, version.

RATIONALE-301: Overall Survival (ITT Analysis Set)

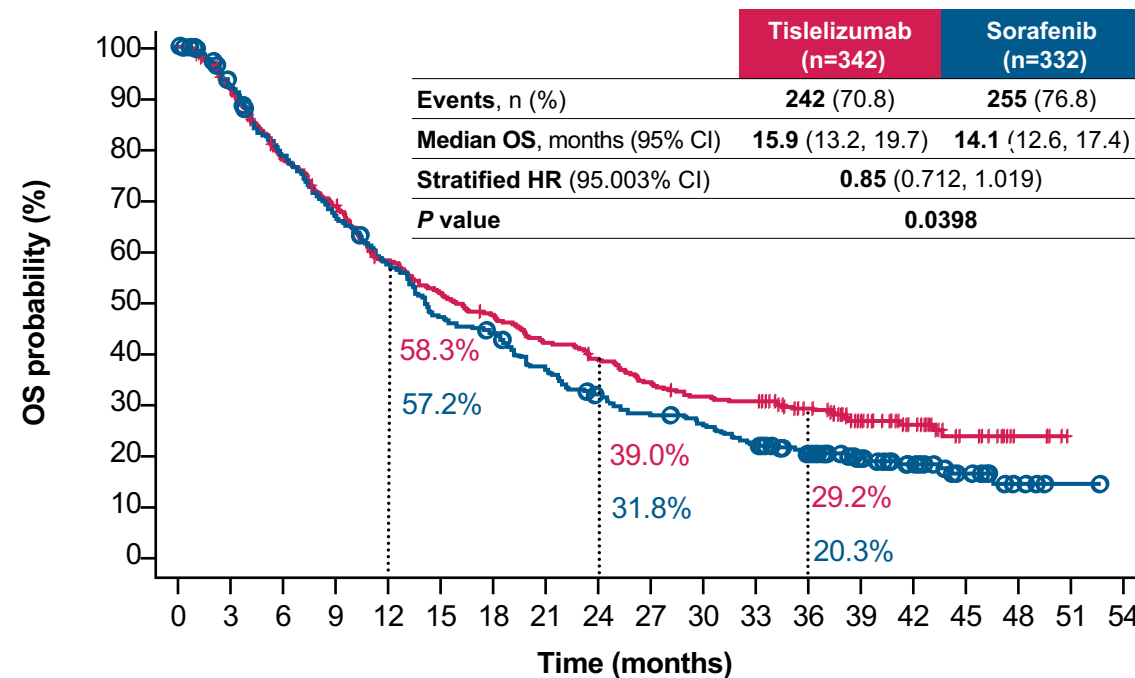
≥65 Years Subgroup



Number of patients at risk:

Tislelizumab	134	122	106	93	75	69	65	55	53	47	46	45	32	20	7	3	0	0	0
Sorafenib	121	104	90	75	62	54	53	42	38	33	29	24	19	13	7	1	1	1	0

Overall Population¹

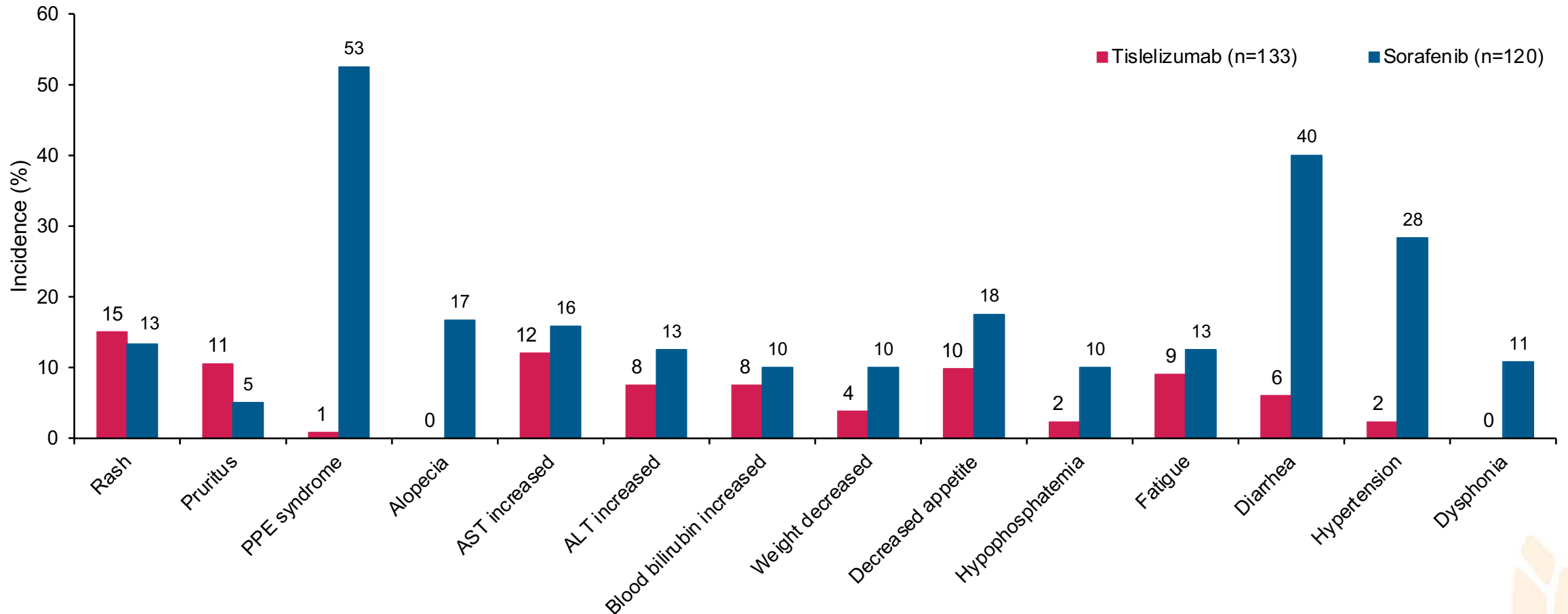


Number of patients at risk:

Tislelizumab	342	307	259	228	191	170	155	137	126	111	101	98	77	53	33	18	4	0	0
Sorafenib	332	291	247	208	179	147	136	113	96	84	77	66	52	39	29	13	4	1	0

- Patients in the ≥65 years subgroup had a numerically longer median OS with tislelizumab vs sorafenib
- Median OS in the tislelizumab arm was longer in the ≥65 years subgroup (18.2 months) than in the overall population (15.9 months), but similar in the sorafenib group (14.2 months and 14.1 months, respectively)¹

RATIONALE-301: Most Common TRAEs in $\geq 10\%$ of Patients in ≥ 65 Years Subgroup (Safety Analysis Set)



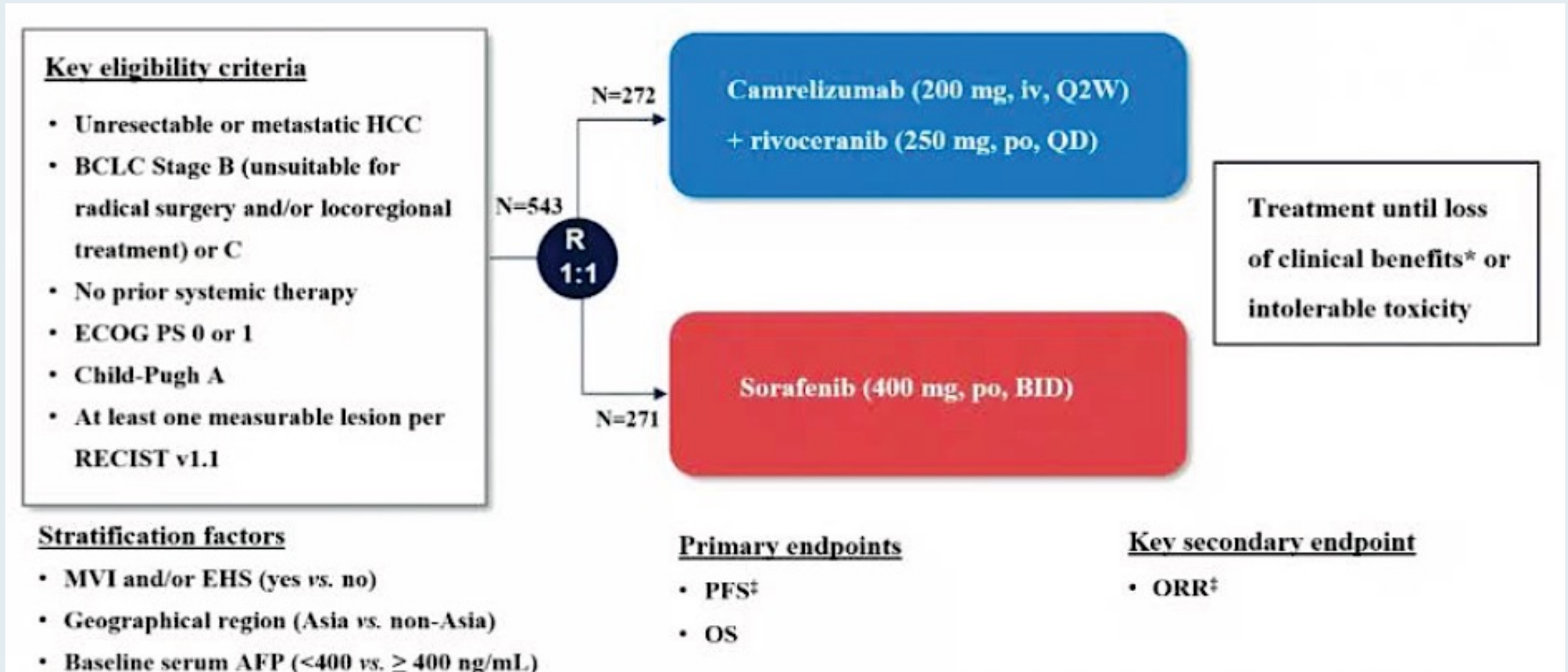
Camrelizumab plus rivoceranib vs. sorafenib as first-line therapy for unresectable hepatocellular carcinoma: a randomized, phase 3 trial

Shukui Qin ^{1,*}, Stephen L. Chan ^{2,*}, Shanzhi Gu ³, Yuxian Bai ⁴, Zhenggang Ren ⁵, Xiaoyan Lin ⁶, Zhendong Chen ⁷, Weidong Jia ⁸, Yongdong Jin ⁹, Yabing Guo ¹⁰, Alexander Sultanbaev ¹¹, Monika Pazgan-Simon ¹², Margaryta Pisetska ¹³, Xiao Liang ¹⁴, Chunxia Chen ¹⁴, Ziqiang Nie ¹⁴, Linna Wang ¹⁴, Ann-Lii Cheng ^{15,†}, Ahmed Omar Kaseb ^{16,†}, Arndt Vogel ^{17,†}

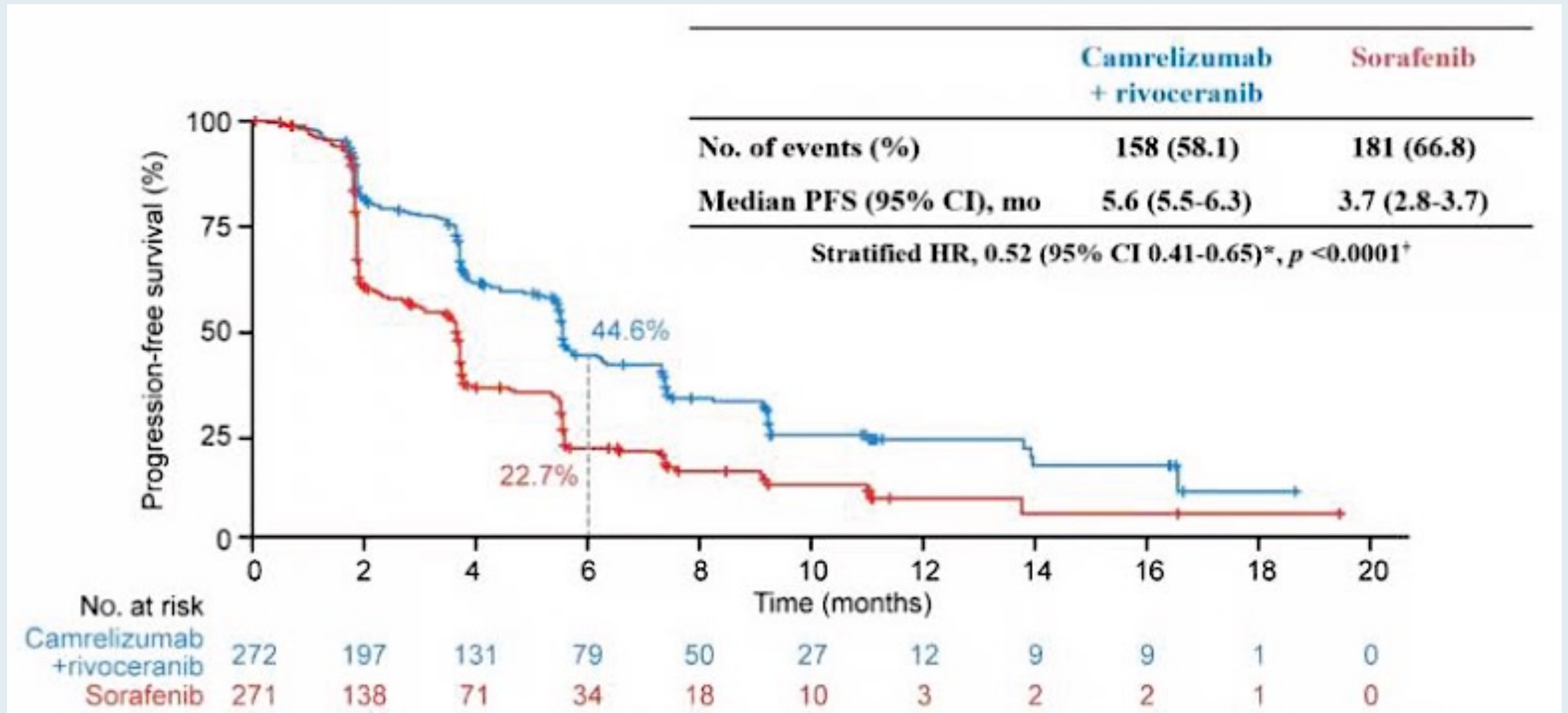
¹ Cancer Center of Jinling Hospital, Nanjing University of Chinese Medicine, Nanjing, China; ² The Chinese University of Hong Kong Medical Center, Shatin, Hong Kong; ³ Hunan Cancer Hospital, Changsha, China; ⁴ The Affiliated Tumor Hospital of Harbin Medical University, Harbin, China; ⁵ Zhongshan Hospital, Fudan University, Shanghai, China; ⁶ Fujian Medical University Union Hospital, Fuzhou, China; ⁷ The Second Affiliated Hospital of Anhui Medical University, Hefei, China; ⁸ Anhui Provincial Hospital, Hefei, China; ⁹ Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China; ¹⁰ Nanfang Hospital, Southern Medical University, Liver Cancer Center, Guangzhou, China; ¹¹ Republican Clinical Oncological Dispensary of the Ministry of Health of the Republic of Bashkortostan, Ufa, Russia; ¹² Centrum Badan Klinicznych, Wroclaw, Poland; ¹³ Communal Non-profit Enterprise "Regional Center of Oncology", Kharkiv, Ukraine; ¹⁴ Jiangsu Hengrui Pharmaceuticals, Co., Ltd, Shanghai, China; ¹⁵ National Taiwan University Hospital, Taipei, Taiwan; ¹⁶ Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany; ¹⁷ M. D. Anderson Cancer Center, Houston, Texas, USA. *Joint first authors. †Joint senior authors.



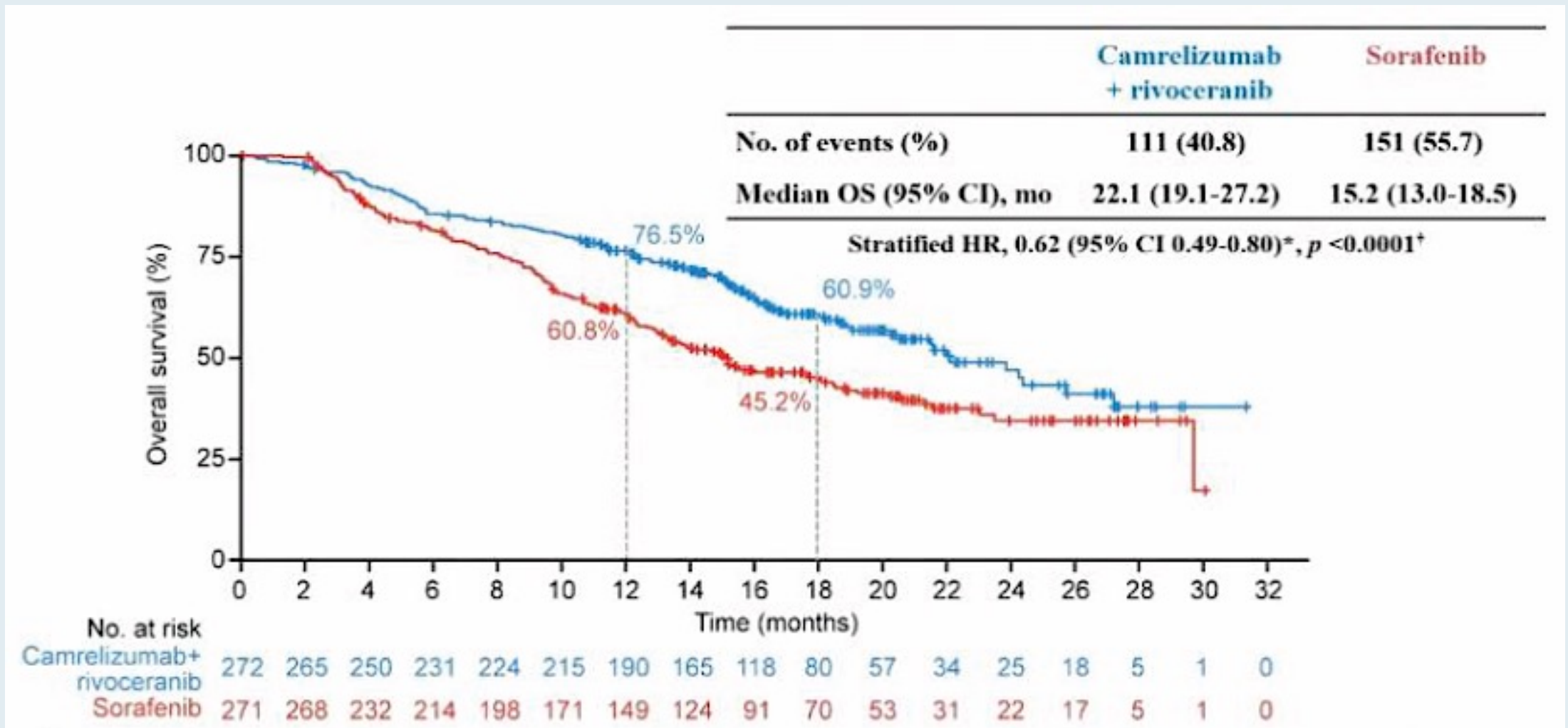
Phase III Trial Schema: First-Line Camrelizumab/Rivoceranib



First-Line Camrelizumab/Rivoceranib: Coprimary Endpoint – PFS



First-Line Camrelizumab/Rivoceranib: Coprimary Endpoint – OS



First-Line Camrelizumab/Rivoceranib: Treatment-Related Adverse Events

Preferred term	Camrelizumab + rivoceranib (N=272)		Sorafenib (N=269)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Hypertension	189 (69.5)	102 (37.5)	116 (43.1)	40 (14.9)
AST increased	147 (54.0)	45 (16.5)	99 (36.8)	14 (5.2)
Proteinuria	134 (49.3)	16 (5.9)	72 (26.8)	5 (1.9)
ALT increased	127 (46.7)	35 (12.9)	80 (29.7)	8 (3.0)
Platelet count decreased	126 (46.3)	32 (11.8)	89 (33.1)	4 (1.5)
Blood bilirubin increased	116 (42.6)	24 (8.8)	75 (27.9)	4 (1.5)
PPE syndrome	102 (37.5)	33 (12.1)	163 (60.6)	41 (15.2)
Diarrhoea	83 (30.5)	6 (2.2)	105 (39.0)	14 (5.2)
RCCEP	79 (29.0)	7 (2.6)	0	0
Neutrophil count decreased	73 (26.8)	16 (5.9)	27 (10.0)	3 (1.1)
White blood cell count decreased	73 (26.8)	7 (2.6)	38 (14.1)	3 (1.1)
GGT increased	66 (24.3)	27 (9.9)	49 (18.2)	20 (7.4)
Hypothyroidism	58 (21.3)	0	16 (5.9)	0

Case Presentation – Dr Abou-Alfa: Case 1

67-year-old lady with history of morbid obesity and diabetes. History of non-alcoholic steatohepatitis that was not monitored short of a reminder on annual medical check ups by her primary physician of elevated liver function tests.

Patient developed abdominal pain back in January 2022. Extensive evaluation showed evident liver mass plus multiple lung lesions. Biopsy of one of the lung lesions showed evident hepatocellular carcinoma.

Case Presentation – Dr Abou-Alfa: Case 1 (Continued)

Son who works as a researcher at a pharmaceutical industry heard of new data of durvalumab plus tremelimumab.

Patient started on durvalumab and had tremelimumab added when it became available.

Patient has been on therapy since. She is now preparing for next visit to Canada Yellowknife in the North Territories taking advantage of the heat wave encompassing the north hemisphere.

Case Presentation – Dr Abou-Alfa: Case 2

72-year-old gentleman with history of hepatitis B on close and regular monitoring with annual liver ultrasound and AFP blood test, was found to have a LI-RAD5 liver lesion, which was resected. Pathology showed evident hepatocellular carcinoma.

Patient was followed with repeat imaging. At some point patient developed shoulder pain. Imaging showed evident bone metastasis.

Patient had extensive imaging including a bone scan. No other sites of disease were noted.

Case Presentation – Dr Abou-Alfa: Case 2 (Continued)

Patient started on pain medications and monthly zoledronic acid.

Patient had an EGD to rule out varices. In absence of varices, patient was started on atezolizumab plus bevacizumab.

While excited about hearing of median overall survival of 19.2 months, at first imaging after about two months on therapy, patient was disappointed to hear of evident progression of disease.

He is bewildered and wonders what to do next?

Agenda

INTRODUCTION: Etiology of Hepatocellular Carcinoma (HCC) and IO Response

MODULE 1: First-Line Therapy for Advanced HCC – Dr Abou-Alfa

MODULE 2: Second- and Later-Line Therapy for Advanced HCC; Emerging Considerations for Patients with Resectable HCC – Dr Li

Second and Later-Line Therapy for Advanced HCC

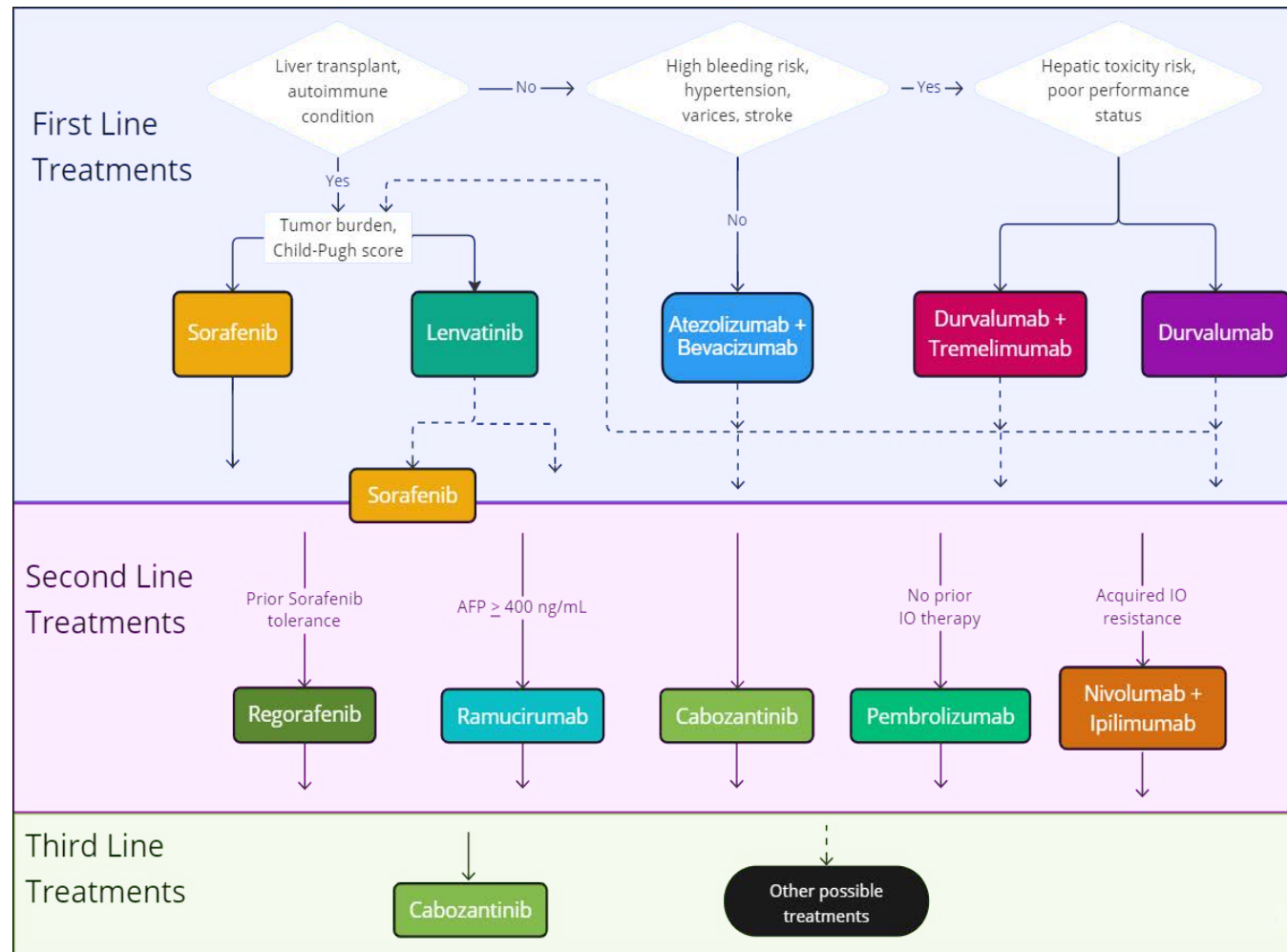
Daneng Li, M.D.

Associate Professor

Department of Medical Oncology and Therapeutics Research

City of Hope Comprehensive Cancer Center

Challenges of HCC Treatment Sequencing



- Interactions between current first-line and proposed second-line treatments are mostly unknown
- No definitive biomarkers that can predict patient response to HCC treatments

FDA-Approved Anti-VEGF-Directed Monotherapy for HCC

Approved line of therapy	Agent	Study	Primary outcomes
First line	Sorafenib¹	Sorafenib vs placebo (N = 602) Phase III SHARP trial	TTP 4.1 mo vs 4.9 mo mOS 10.7 mo vs 7.9 mo
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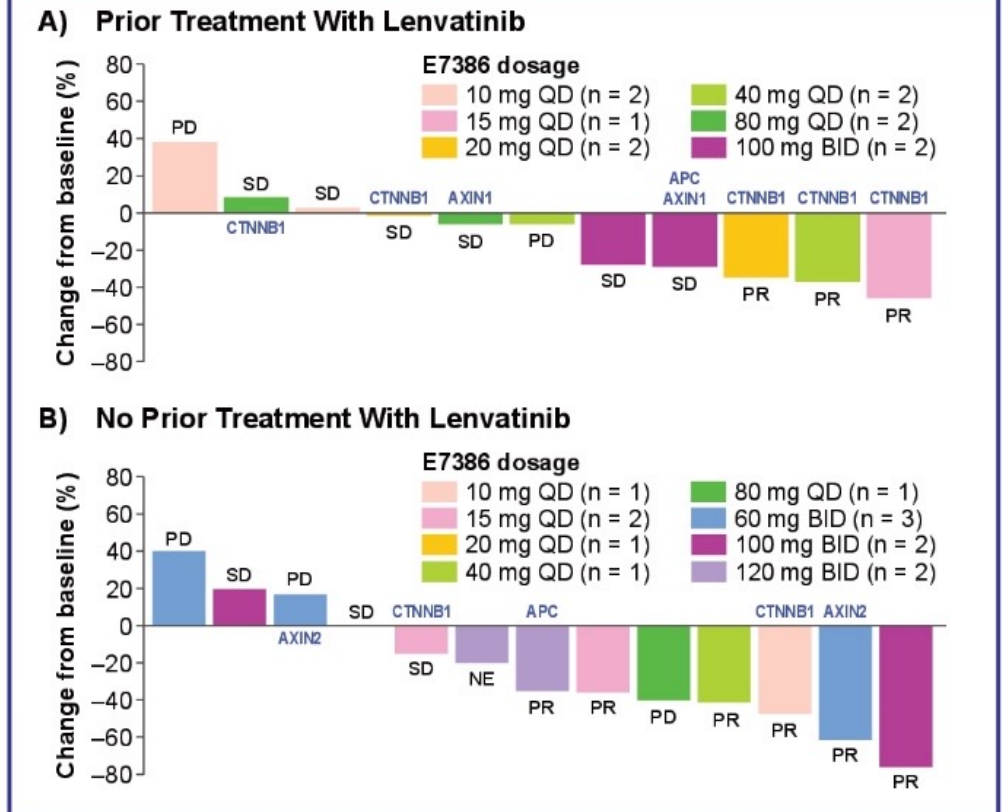
TTP = time to progression; mPFS = median progression-free survival; mOS = median overall survival

¹ Llovet JM et al. *N Engl J Med* 2008;359(4):378-90; ² Kudo M et al. *Lancet* 2018;391(10126):1163-73; ³ Bruix J et al. *Lancet* 2017;389(10064):56-66; ⁴ Abou-Alfa GK et al. *N Engl J Med* 2018;379(1):54-63; ⁵ Zhu AX et al. *Lancet Oncol* 2019;20(2):282-96.

Phase 1b Trial: E7386 + Lenvatinib

- E7386 blocks interaction between CREB-binding protein β -catenin and modulates Wnt/ β -catenin signaling
- Combination E7386 plus lenvatinib demonstrated promising anti-tumor activity, even among patients who previously received Lenvatinib (3/11, ORR 27%)

Figure 3. Tumor Responses in Patients With (A) and Without (B) Prior Lenvatinib Treatment



One patient discontinued treatment before tumor assessment and is not included in this figure. Selected Wnt signaling mutations (based on ctDNA analysis) are shown in blue. BID, twice daily; C#D#, cycle # day #; CR, complete response; ctDNA, circulating tumor DNA; NE, not evaluable; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease.

Regorafenib: Updates from the Observational REFINE Study

- Upfront dose reductions were common in this real-world analysis
 - Differences in dosing may be associated with liver function and differences in clinical practice between Asian and non-Asian countries
 - Median OS was longer in patients who started treatment at 160 mg/day compared to patients who had upfront dose reductions
- TEAE incidence similar between US and global cohorts
 - Diarrhea and hand-foot skin reaction were less common in US patients

	All Patients (n=1005)	US Cohort (n=65)
Median OS, months (95% CI)	13.2 (11.6-14.8)	11.4 (8.4-18.0)
Median duration of treatment, months (range)	3.7 (<0.1-38.9)	3.1 (<0.1-24.6)
Any-grade TEAE, %	92	91
TEAE leading to dose modification, %	45	38

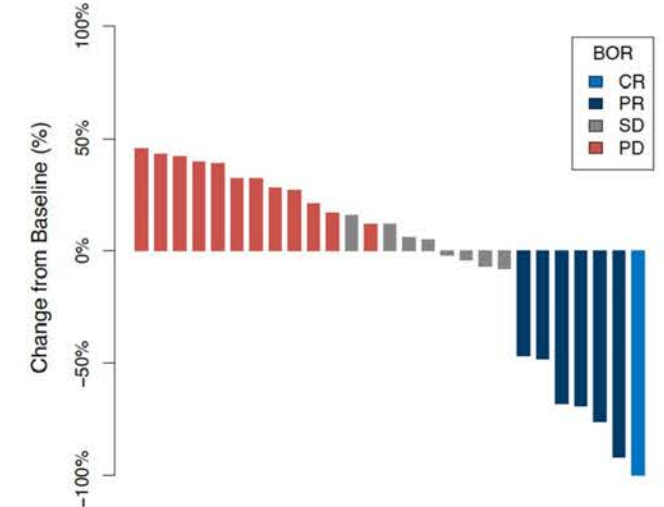
IO After Prior Anti-PD-(L)1 Treatment

Ipilimumab + Nivolumab After Prior Immune Checkpoint Inhibitor (ICI) Therapy

Patient Characteristics (n=32)	n (%)
Median age (range), years	67.0 (43.0-80.0)
Prior ICI therapy	
Atezolizumab plus bevacizumab	16 (50)
Other VEGF plus ICI combination	10 (31)
Immune checkpoint monotherapy	6 (19)
Lines of systemic therapy prior to ipilimumab plus nivolumab	
1	10 (31)
2	15 (47)
3+	7 (22)

Summary of Patient Responses	n=32
mOS, months (95% CI)	9.2 (5.9-NR)
mPFS, months (95% CI)	2.9 (2.1-NR)
ORR, % (n)	22 (7)
DCR, % (n)	47 (15)

Figure 1. Target Lesion Change and Objective Response



Percent change in patient target lesion(s), determined by investigator review of pre- and post-treatment imaging, with best overall response using RECIST v1.1.

- Data suggest ipilimumab + nivolumab can improve outcomes in advanced HCC patients who had prior ICI treatment
- Of note, all patients who had an objective response to ipilimumab + nivolumab had not had an objective response on prior anti-PD-(L)1 treatment
- Progression on prior anti-PD-(L)1 therapy may not preclude treatment with ipilimumab + nivolumab

Ongoing Trials: Immunotherapy Post-Atezolizumab + Bevacizumab

Emerging Considerations for Patients with Resectable HCC

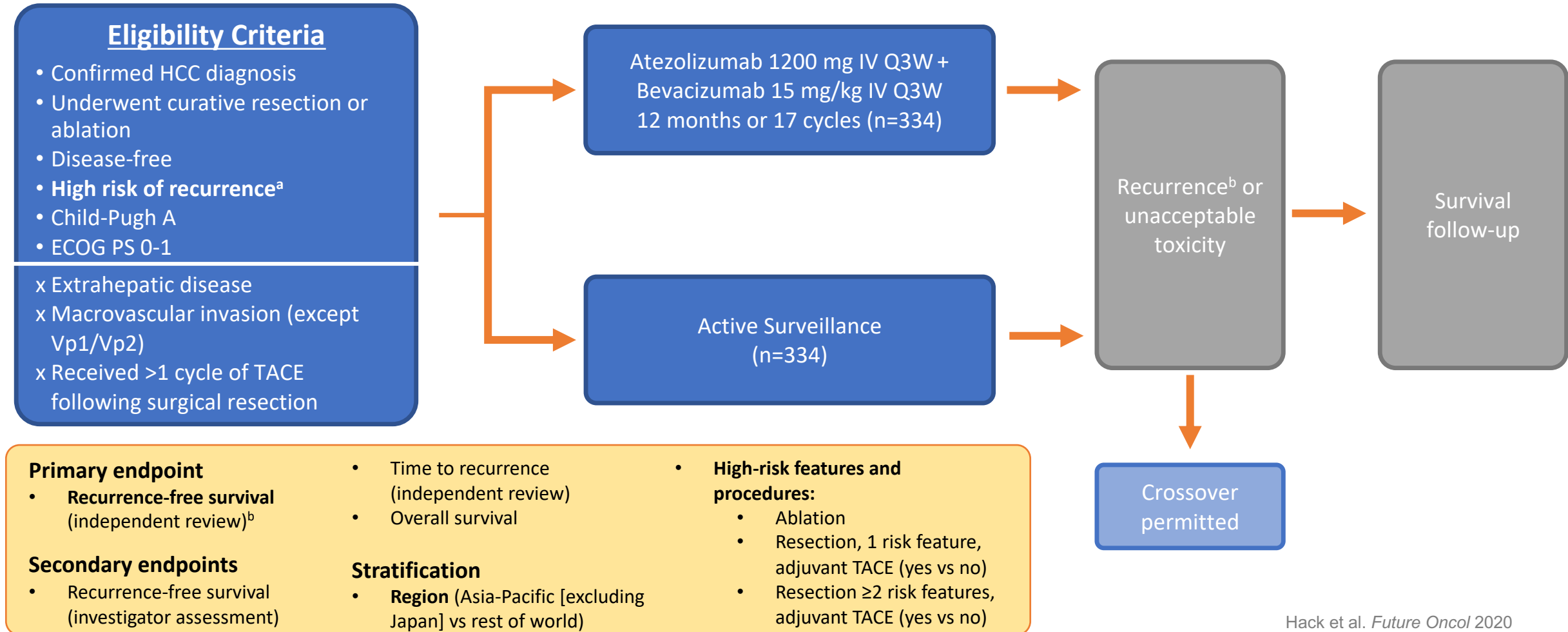
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Department of Medical Oncology and Therapeutics Research

City of Hope Comprehensive Cancer Center

IMbrave050: Adjuvant Atezolizumab + Bevacizumab



^a **High-risk features:** tumor >5 cm, >3 tumors, microvascular invasion, minor macrovascular invasion Vp1/Vp2, or Grade 3/4 pathology.

^b Intrahepatic recurrence defined by EASL criteria. Extrahepatic recurrence defined by RECIST 1.1.

IMbrave050: Baseline Characteristics

	Atezo + Bev (n=334)	Active Surveillance (n=334)
Median age (range), years	60 (19-89)	59 (23-85)
Male sex, n (%)	277 (82.9)	278 (83.2)
Ethnicity, n (%)		
Asian	276 (82.6)	269 (80.5)
White	35 (10.5)	41 (12.3)
Other	23 (6.9)	24 (7.2)
Geographic region, n (%)		
Asia-Pacific, excluding Japan Rest of world	237 (71.0) 97 (29.0)	238 (71.3) 96 (28.7)
ECOG PS score, n (%)		
0 1	258 (77.2) 76 (22.8)	269 (80.5) 65 (19.5)
PD-L1 status, n (%) ^{a, b}		
≥1% <1%	154 (54.0) 131 (46.0)	140 (50.2) 139 (49.8)

	Atezo + Bev (n=334)	Active Surveillance (n=334)
Etiology, n (%)		
Hepatitis B	209 (62.6)	207 (62.0)
Hepatitis C	34 (10.2)	38 (11.4)
Non-viral Unknown	45 (13.5) 46 (13.8)	38 (11.4) 51 (15.3)
BCLC stage at initial diagnosis, n (%)		
0	2 (0.6)	3 (0.9)
A	287 (85.9)	277 (82.9)
B	25 (7.5)	32 (9.6)
C	20 (6.0)	22 (6.6)

Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo. BCLC, Barcelona Clinic Liver Cancer.

^a n=285 for atezo + bev and 279 for active surveillance. ^b PD-L1 expression is defined as the total percentage of the tumor area covered by tumor and immune cells stained for PD-L1 using the SP263 immunohistochemistry assay (VENTANA).

Kudo et al. 2023 ASCO abstract 4002
Chow et al. 2023 AACR abstract CT003

Courtesy of Daneng Li, MD

IMbrave050: Curative Procedures

	Atezo + Bev (n=334)	Active Surveillance (n=334)
Resection, n (%)	293 (87.7)	292 (87.4)
Longest diameter of the largest tumor at diagnosis, median (range), cm ^a	5.3 (1.0-18.0)	5.9 (1.1-25.0)
Tumors, n (%)		
1	266 (90.8)	260 (89.0)
2	20 (6.8)	29 (9.9)
3	4 (1.4)	2 (0.7)
4+	3 (1.0)	1 (0.3)
Adjuvant TACE following resection, n (%)	32 (10.9)	34 (11.6)
Any tumors >5 cm, n (%)	152 (51.9)	175 (59.9)
Microvascular invasion present, n (%)	178 (60.8)	176 (60.3)
Minor macrovascular invasion (Vp1/Vp2) present, n (%)	22 (7.5)	17 (5.8)
Poor tumor differentiation (Grade 3 or 4), n (%)	124 (42.3)	121 (41.4)

	Atezo + Bev (n=334)	Active Surveillance (n=334)
Ablation, n (%)	41 (12.3)	42 (12.6)
Longest diameter of the largest tumor at diagnosis, median (range), cm	2.5 (1.2-4.6)	2.6 (1.5-4.6)
Tumors, n (%)		
1	29 (70.7)	31 (73.8)
2	11 (26.8)	8 (19.0)
3	1 (2.4)	3 (7.1)

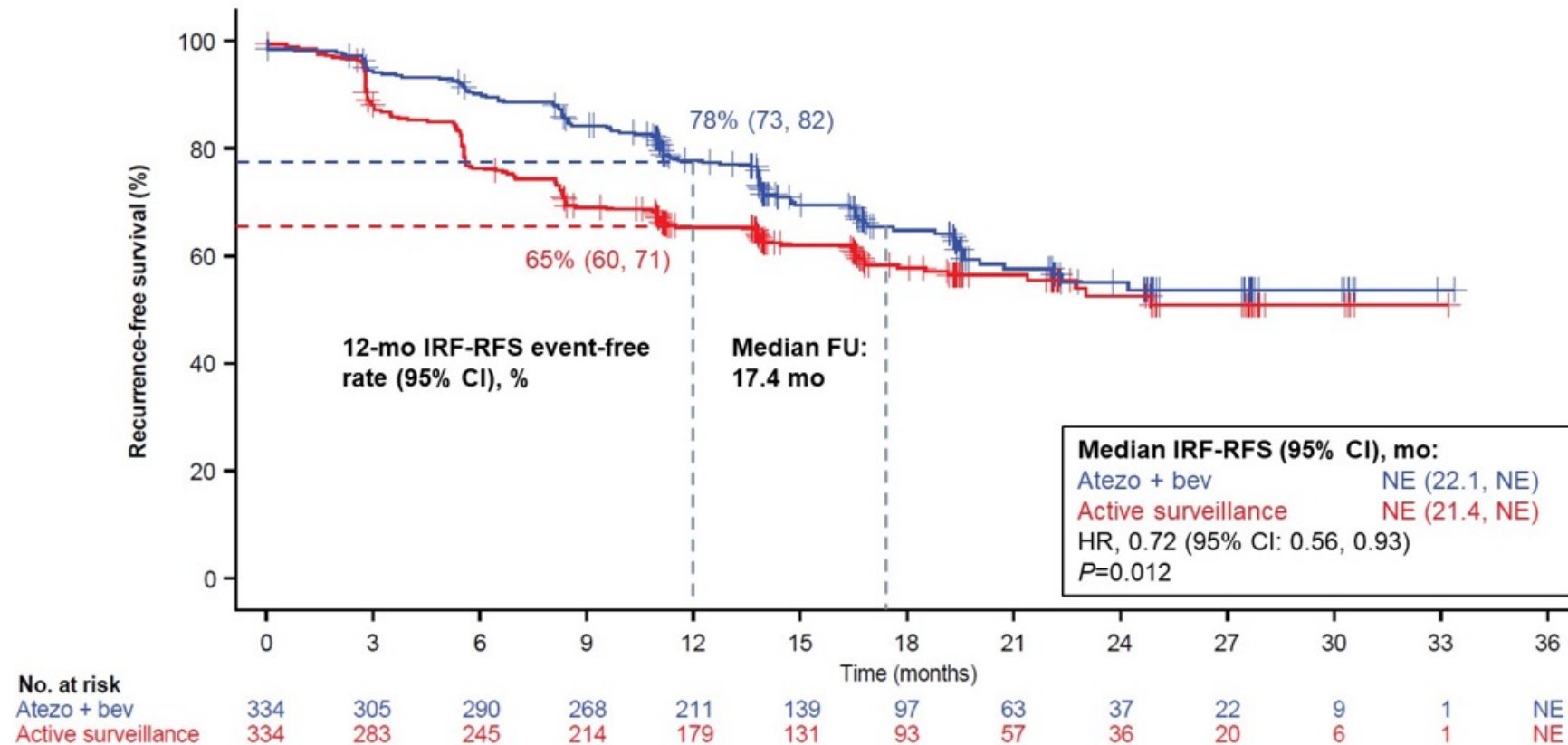
Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo.

^a 1 patient in the atezo + bev arm was excluded from the calculation due to data entry error.

Kudo et al. 2023 ASCO abstract 4002
Chow et al. 2023 AACR abstract CT003

Courtesy of Daneng Li, MD

IMbrave050: Recurrence-free Survival



- Adjuvant atezolizumab + bevacizumab prolongs recurrence-free survival compared to active surveillance

IMbrave050: Safety

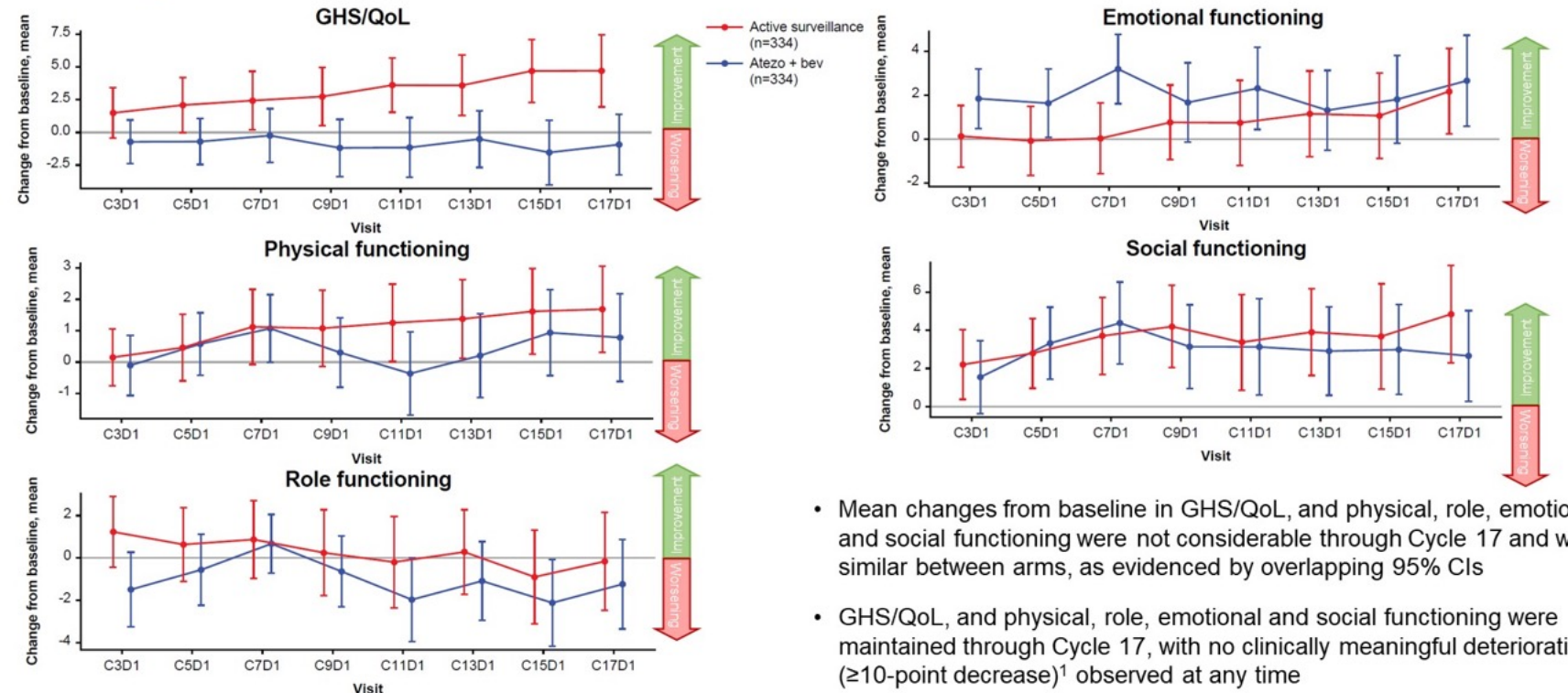
- Common AEs: proteinuria, hypertension, platelet count decreased, aspartate aminotransferase increased, alanine aminotransferase increased
- Grade 5 AEs (Atezo/Bev arm): 1 case of esophageal varices hemorrhage related to atezo/bev and 1 case of ischemic stroke related to bev

	Atezo + Bev n (%) (n=332)	Active Surveillance n (%) (n=330)
Median treatment duration, months	Atezo: 11.1 Bev: 11.0	N/A
Any-grade AE	326 (98.2)	205 (62.1)
Treatment-related	293 (88.3)	N/A
Grade 3/4 AE	136 (41.0)	44 (13.3)
Treatment-related	116 (34.9)	N/A
Serious AE	80 (24.1)	34 (10.3)
Treatment-related	44 (13.3)	N/A
Grade 5 AE	6 (1.8)	1 (0.3)
Treatment-related	2 (0.6)	N/A
AE leading to dose interruption of any study treatment	155 (46.7)	N/A
AE leading to withdrawal of any study treatment	63 (19.0)	N/A

IMbrave050: Patient-Reported Outcomes

- Baseline QOL scores similar between treatment arms and comparable to general population
- No significant difference in various QOL domains between treatment arms over time

Change from baseline in IL42–EORTC QLQ-C30 scales



Clinical cutoff: October 21, 2022; median follow-up duration: 17.4 mo.
1. Osoba et al. J Clin Oncol 1998;16:139-44.

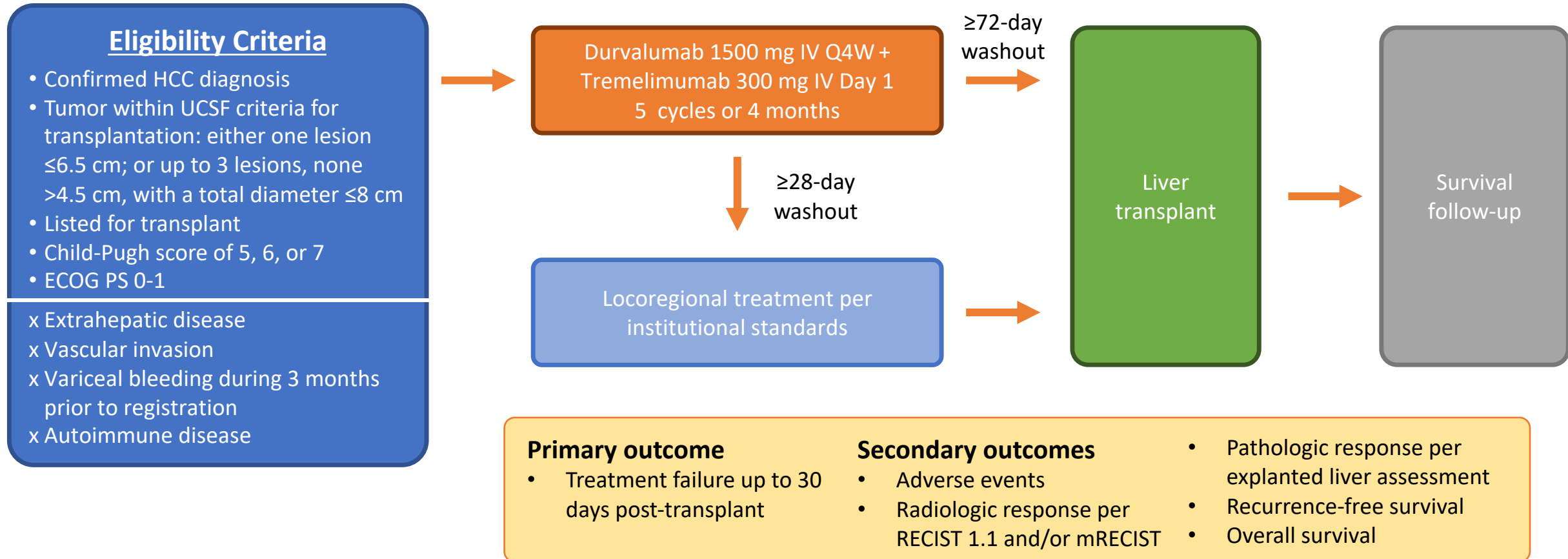
- Mean changes from baseline in GHS/QoL, and physical, role, emotional and social functioning were not considerable through Cycle 17 and were similar between arms, as evidenced by overlapping 95% CIs
- GHS/QoL, and physical, role, emotional and social functioning were maintained through Cycle 17, with no clinically meaningful deterioration (≥ 10 -point decrease)¹ observed at any time

Ongoing Trials: Adjuvant Immunotherapy

Neoadjuvant Immunotherapy Pre-Transplant: Considerations

- Immunotherapy has shown positive results in unresectable HCC patients; neoadjuvant treatment could downstage disease and increase the number of HCC patients eligible for liver transplant
- However, graft rejection is a major concern
- A literature search by Woo et al. identified 45 patients who received neoadjuvant anti-PD-(L)1 immunotherapy followed by liver transplant¹
 - Mixed results in terms of graft rejection and disease recurrence
 - Rejection in 11 of 45 patients
 - Recurrence in 2 of 45 patients
 - Considerations to investigate further: length of washout period between immunotherapy and transplant, PD-(L)1 expression in donor tissue, relationship between pre-transplant immunotherapy and post-transplant immunosuppressive regimen

Durvalumab + Tremelimumab in HCC Patients Listed for Liver Transplant (NCT05027425)



Ongoing Trials: Neoadjuvant Immunotherapy in HCC Patients Planned for Liver Transplant

Case Presentation – Dr Li: Case 1

- 84-year-old gentleman with history of Hepatitis B presented for evaluation for abdominal pain
- PMH: Type 2 Diabetes, Hyperlipidemia, Hypertension, chronic Hepatitis B
- CT CAP imaging revealed a large lobulated 6.8x6.3x4.7 cm heterogenous mass involving the medial inferior right hepatic lobe, extending medially to or originating from the right adrenal gland with possible invasion to IVC, satellite liver lesions also noted
- Liver biopsy performed consistent with moderately to poorly differentiated HCC

Case Presentation – Dr Li: Case 1 (Continued)

- Patient underwent EGD with no evidence of significant esophageal varices
- Labs notable for Albumin of 3.3 g/dL, T.bili of 1.0mg/dL, INR of 1.0, AFP 100 ng/mL
- Patient started on 1st line treatment with Atezolizumab plus Bevacizumab
- Patient underwent 3 cycles of treatment with initial treatment response on CT imaging with tumor shrinkage of liver masses
- After 9 cycles of treatment, there was evidence of disease progression

Case Presentation – Dr Li: Case 1 (Continued)

- Patient was started on 2nd line therapy with sorafenib dose reduced at 200mg BID, course was complicated by hyperammonemia requiring treatment with lactulose
- Follow up imaging at 2 months was notable for disease progression
- Patient was started on treatment with Nivolumab plus Ipilimumab as 3rd line therapy
- Patient completed 4 cycles of Nivolumab plus Ipilimumab with treatment response on imaging, continued with Nivolumab q2week maintenance therapy
- After 2 months of Nivolumab maintenance therapy, there was evidence of new neck mass consistent with disease progression but otherwise stable liver lesions

Case Presentation – Dr Li: Case 1 (Continued)

- Patient underwent RT to symptomatic neck mass and continued on Nivolumab maintenance therapy
- After additional 2 months of Nivolumab maintenance therapy, patient developed further progression with new pulmonary metastasis
- Patient started on 4th line therapy with cabozantinib at 60mg daily
- After 3 weeks of treatment, patient developed significant fatigue, cabozantinib held for 2 weeks with improvement in fatigue and cabozantinib resumed with dose reduction of 40mg daily
- Recent imaging at 2 months shows overall stable disease

Case Presentation – Dr Li: Case 2

- 66-year-old female with history of infertility, acid reflux who presented with abdominal pain
- Denies any history of hepatitis, alcohol or obesity
- CT CAP imaging shows a 13 cm right hepatic lobe lesion with small associated 1.4cm lesion in the same lobe
- CT guided biopsy shows moderately to poorly differentiated HCC
- Labs include Albumin of 4.0 g/dL, T.bili of 0.7mg/dL, INR of 1.0, AFP 400 ng/mL

Case Presentation – Dr Li: Case 2 (Continued)

- Patient underwent right sided hepatectomy without complications
- Pathology shows Poorly differentiated (G3) HCC measuring up to 14.5cm with microvascular invasion, surgical margins negative
0/2 regional lymph nodes sampled were negative for malignancy
- Should this patient be treated with adjuvant Atezolizumab plus Bevacizumab?

Inside the Issue: Exploring the Current and Future Management of High-Risk, Hormone-Sensitive Nonmetastatic Prostate Cancer

A CME/MOC-Accredited Live Webinar

Monday, July 31, 2023

5:00 PM – 6:00 PM ET

Faculty

Neal D Shore, MD

Mary-Ellen Taplin, MD

Moderator

Neil Love, MD

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